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BULLETIN ON NARCOTICS

Vol. VI, No. 1, JANUARY-APRIL 1954

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Bulletin on NARCOTICS

Vol. VI, No. 1, JANUARY-APRIL 1954

UNITED NATIONS

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GENERAL

The Traffic in Narcotics*

An interview with the Hon. Harry J. Anslinger
United States Commissioner of Narcotics

The Honourable Harry J. Anslinger, Federal Commissioner of Narcotics for the United States of America, has just published, in collaboration with William F. Tompkins, United States attorney for the district of New Jersey, a book entitled The Traffic in Narcotics *(Funk and Wagnalls Co., New York, 1953).*

The experience and wide knowledge of the question that Mr. Anslinger has brought to this work make this book a very important one for all those concerned with the problem, and the editors of the Bulletin on Narcotics *considered that the following interview with him, dealing with the most important statements in the book, would be of general interest.*

Q. When you chose the title for your book, *The Traffic in Narcotics*, am I right to assume that you had in mind primarily the illicit trade?

A. Not exactly, since I deal with the licit trade as well, but unfortunately the illegal aspect of the traffic is by far the most troublesome, since addicts are almost in all cases supplied by it.

Q. Do you think drug addiction is a specific mark of contemporary life?

A. By no means: for centuries the poppy has been the instrument of unprincipled men who by it satisfied their lust for wealth and power, of nations who used it for amoral reasons and as a potent weapon of aggression.

The character of drug addiction being different in different regions of the world, we do not have adequate, up-to-date and comparable information regarding its extent.

The international community organized the struggle against the narcotics evil by concluding a series of international treaties in this field and by creating organizations entrusted with the application of these instruments: a policy-making body, which was called the Advisory Committee of the League of Nations (now the Commission on Narcotic Drugs of the Social and Economic Council of the United Nations); a body in charge of the control of international statistics relating to legitimate manufacturing of, trade in, and consumption of narcotics, the Permanent Central Opium Board; a body in charge of estimating the world's legitimate needs in narcotics, the Supervisory Body.

Q. How effective were the opium conventions?

A. The machinery established by the Supervisory Body emerged from its initial trial in 1933 with considerable success. Estimates were received that year for 45 countries (including 14 countries which had not ratified the Convention) and for 83 colonies, protectorates and territories. The Supervisory Body was called upon to provide estimates for 23 countries and 31 colonies for which no estimates had been furnished. For 1952. estimates were furnished by 73 governments and 78 territories, and the Supervisory Body was called upon to provide estimates for only 10 countries and 6 territories.

The effectiveness of the Committee is attested to by the fact that in its first year of working it succeeded in reducing the total amount of morphine required for all purposes (in 1934) by more than three tons.

But the main international body was the Advisory Committee.

Q. Do you think the Advisory Committee really succeeded in checking the illicit trade?

A. As the result of the Opium Advisory Committee's turning the pitiless spotlight of the world press on specific narcotic conditions from time to time, it was able to drive the illicit traffic from France, Switzerland, Holland, Bulgaria and Yugoslavia. It repeatedly exposed the manner in which loose controls over manufacture, and lack of effective laws had encouraged the building up of large scale illicit trafficking in these countries.

Q. I understand that a new single convention is in the making, in addition to the existing eight international agreements on narcotics. In your view what should be the purpose of this new single convention?

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A. The object of the proposed unification is not only to combine the eight international agreements on the subject, but also to revise and strengthen these agreements, closing loopholes and rejecting obsolete provisions. It is obviously most desirable to revise these international agreements, one of which dates back to 1912, and to incorporate them if possible into a single agreement which will provide reasonably effective control in these main fields: the production of opium, coca leaves and cannabis; the manufacture of the dangerous or potentially dangerous products of these substances as well as of synthetic substitutes for them; and the distribution of such raw material and of the manufactured products or synthetic substitutes.

Q. From 1909, when the United States convened the Shanghai Conference, the United States has always taken a considerable part in the international struggle. A good example of this activity is the effort to abolish the opium monopolies in the Far East. Apart from its general humanitarian purpose, what was the immediate practical reason for the efforts of the United States during the Second World War towards abolishing the opium monopolies, and what was the result of this effort?

A. From the standpoint of the health and safety of the men of the armed forces of the United States, the government was convinced that it was imperative, immediately upon the occupation by the United States forces of a part or the whole of any one of the Japanese-occupied territories, to seize all drugs intended for other than medical and scientific purposes. American expeditionary forces under American command were therefore instructed to close existing opium monopolies, opium shops and dens. That was the immediate problems.

As a result of these discussions the United States Government on 21 September 1942 addressed an *aide-mémoire* to the United Kingdom, the Netherlands and other interested governments on this subject. On 10 November 1943, the United Kingdom and Netherlands Governments announced their intentions to abolish the legalized sale of opium in their Far Eastern territories, and similar action was later taken by the Governments of France and Portugal. Opium smoking has now been declared illegal in all parts of the world except in Thailand.

Q. In order to be able to participate usefully in the international struggle, it seems that a country should first establish its own control: what are the principal measures for the control of narcotics in the United States?

A. The three principal federal statutes controlling the substances under discussion are the Harrison Narcotic Law, as amended, now incorporated in the Internal Revenue Code; the Marihuana Tax Act, as amended, also incorporated in the Internal Revenue Code; and the Act of May 26th 1922, as amended, known as the Narcotic Drugs Import and Export Act.

Sales or transfers of narcotic drugs are limited generally to those made pursuant to official order forms obtainable, in blank, by registrants, from the Director of Internal Revenue. Exception from the order from requirement is made in favour of dispensing to a patient by a qualified practitioner in the course of his professional practice only, provided, however, that such physician, dentist or veterinary surgeon shall keep a record of all such drugs dispensed or distributed. The record must include the amount dispensed, the date, the name and address of the patient to whom the drugs are dispensed, except in cases where the drugs are dispensed by the physician in the course of personal attendance. Another important exception from the requirement of the Act is found in the case of a sale by a druggist to or for a patient, pursuant to a lawful written prescription issued by a qualified physician, dentist or veterinary surgeon. Penalties are provided for violation of the Act and the Secretary of the Treasury is given the power to make, prescribe and publish all the needed rules and regulations for carrying the provisions of this Act into effect. This Act is designed to direct the manufacture and distribution of narcotic drugs through medical channels to consumption use for medical or scientific purposes only.

Q. What are the main provisions of the Narcotic Drugs Import and Export Act?

A. This Act authorizes the importation only of such quantities of opium and coca leaves as the Commissioner of Narcotics shall find to be necessary to provide for medical and scientific needs under such regulations as the Commissioner shall prescribe. Importation of any form of narcotic drugs except such limited quantities of crude opium and coca leaves for medical and scientific uses is prohibited. The importation of smoking opium or opium prepared for smoking is specifically prohibited, and possession of such opium is made prima facie evidence of an offense. The aim of this latter section is to stamp out the use of narcotics in this country except for legitimate medical purposes. While numerous attacks have been made on the validity of this section, the courts have held that under the power accorded it by the Constitution, Congress had the power to regulate foreign commerce to create the presumption contained therein. The Act also permits exportation of manufactured drugs and preparations under a rigid system of control designed to assure their use for medical needs only in the country of destination.

Q. What are the main provisions in the United States concerning the dispensing of drugs by physicians and druggists?

A. A physician who intends to practice medicine and to administer or dispense narcotic drugs in the course of such practice must apply for registration under the Harrison Law with the Director of Internal Revenue of the district in which he proposes to prac-

tice, and must pay the appropriate occupational tax for the fiscal year applicable. Before being entitled to such registration, however, he must be lawfully entitled under the laws of the state or territory or district wherein he intends to practice, to distribute, dispense, give away or administer narcotic drugs to patients upon whom he, in the course of his professional practice, is in attendance [26 U.S.C. 3220]. In the case of a medical practitioner, this requirement usually means that the applicant is a physician who holds an unrevoked and unrestricted license to practice medicine in the particular state, territory or district.

The right to register and pay tax under the federal statute depends on the right to dispense under the state laws.

The provisions of the law are substantially the same for a druggist.

Q. The agency in charge of the implementation of these Acts is the Bureau of Narcotics. What are its main duties?

A. The duties of the Bureau include the investigation, detection, and prevention of violations of the federal narcotic laws (including the federal Marihuana Law and the Opium Poppy Control Act of 1942), the determination of quantities of crude opium and coca leaves to be imported into the United States for medical and legitimate uses, and the issuance of permits to import the crude narcotic drugs and to export drugs and preparations manufactured therefrom under the law and regulations. An annual report is made to Congress which also serves the purpose of the report in behalf of the Government for transmittal through the State Department to the nations signatory to the International Drug Conventions of 1912 and 1931.

Q. Is it true that your Bureau has the possibility of buying information concerning the illicit traffic?

A. By special statute approved 3 July 1930, the Commissioner of Narcotics is authorized and empowered to pay to any person from funds appropriated for the enforcement of the federal narcotic laws of the United States, for information concerning a violation of any narcotic law resulting in a seizure of contraband narcotics, such sum as he may deem appropriate.

Q. What has been in your opinion the general trend of narcotic abuse in the last generation?

A. The federal narcotic laws and the state narcotic laws have been in force for only a generation. Throughout that period and until just recently there had been a steady, substantial decline in addiction. It coincided with the enforcement of penal narcotic laws. There was a deviation from a straight decline in a rather sharp upsurge after the First World War, but that soon subsided. In the early 1920's, heroin and morphine were available at $25 to $50 an ounce. A few unscrupulous doctors were writing prescriptions for narcotics in large amounts. Drugs were smuggled into the country in trunk lots. It was common for addicts to have tremendous habits: 5, 10, 20, or even 50 grains of morphine a day! Today, the unscrupulous doctor has almost disappeared. The occasional cheater dares to prescribe a few grains only instead of ounces. Wholesale diversions are non-existent except for an occasional bona-fide robbery or burglary. Smuggling is in small amounts that can be concealed on the person.

Q. The laws on narcotics being somewhat complicated, the physician and druggist find it probably difficult to observe them; can you indicate a few rules which, in your opinion, should help in the interpretation of the narcotics statutes?

A. A physician could avoid the pitfalls attendant to criminal and civil liability if the following fundamental rules were observed:

1. Secure a complete history of the ailment;
2. Make a complete and thorough physical examination in every case;
3. Ascertain whether the illness requires narcotics and good medical practice demands their prescription;
4. Use non-habit-forming drugs instead of opiates wherever possible;
5. Beware of strangers and itinerant patients who suggest their need for drugs;
6. Remember always that improper and prolonged dosages can cause an individual to become an addict;
7. Do not write a prescription for office use. That supply should be secured on a drug order form.

Druggists should consider the following suggestions:

1. Refuse to compound an improperly prepared prescription;
2. Make no delivery of a telephone prescription without receiving a properly prepared prescription before delivery of the narcotic is made;
3. Never sell a narcotic drug except upon prescription;
4. Remember that narcotic prescriptions may not be refilled;
5. Be familiar with the quantities a customer is using; exorbitant quantities over a long period should warrant close scrutiny.

Q. The public is sometimes under the impression that drug addicts are unfortunates who have been slaves to an evil habit which anyone is liable to contract. Is this correct?

A. Too infrequently are we told that the chances of a complete cure are not good, that those addicted a relatively short time represent most of those cured, and that relapse is frequent. Too infrequently are we advised that we are in the main not dealing with average citizens who have suddenly been smitten by drug addiction, but in fact with people who had

unpleasant and troublesome tendencies before drug addiction was superimposed. And too infrequently are we informed that many cases warrant strong corrective action because of some basic disturbance which drugs have awakened, or simply because of prior antisocial behaviour. A spot check of any police record bureau will disclose the fact that many addicts were criminal offenders long before taking on the drug habit. Make no mistake about it—we are not dealing with something hospitalization alone will cure but a dreaded scourge that penetrates infinitely deeper and requires a much greater effort to uproot. And in too many cases, we are confronted with some inherently bad patients.

Q. Could you give a figure, however rough, of the estimated number of drug addicts in the United States from 1877 up to now?

A. Three-quarters of a century ago, narcotics addiction in the United States was almost eight times as prevalent as it is today. In 1877, the estimated number of narcotic users was 1 in every 400 of the population.

When the Harrison Act was passed in 1914, there were perhaps 150,000 to 200,000 narcotic addicts in the United States, or about 1 in every 460. Remedial legislation had the effect of scaling down addiction until the First World War, when only 1 man in 1,500 drafted was found to be a drug addict. There was a deviation from a straight decline in a rather sharp upsurge after the First World War, and in 1924 it was estimated by the United States Public Health Service that there was 1 addict in every 1,000 of the population.

As the result of vigorous enforcement of the federal narcotic laws, the figure dropped to 1 man in 10,000 in the Second World War. When that war ended, addiction was probably at the irreducible minimum. A temporary upswing in addiction occurred again in the post-war period, as predicted by the Federal Bureau of Narcotics.

Q. How should the addict be treated?

A. Proper treatment dictates that the drugs be withdrawn humanely and gradually from the patient, followed by rehabilitative and psychiatric treatment. Generally the best plan for withdrawal involves the substitution of methadon for whatever drug the addict has been using, followed by a reduction of the dosage of methadon over a period of approximately ten days.

After withdrawal has been accomplished, any chance of cure requires a prolonged period of institutional rehabilitation under closest surveillance. The individual should be enabled to engage in useful work each day and occupational therapy should be geared to bring out and implement any talents or skills which are present. It is important that all patients, including those with chronic diseases, be required to participate in some type of useful endeavour. Recreational facilities, such as movies, athletics, games, reading rooms and music, should also be provided.

Psychotherapy, of great importance in the effort to avoid relapse, must be adequate. The treatment parallels that given to non-addicted persons suffering from psychoneuroses and other character disorders with a view to obtaining as high a degree of mental and emotional stabilization as possible. Unfortunately, adequate personnel is lacking to care for all those who require psychotherapy.

Q. What principles would you recommend in any anti-narcotics campaign?

A. Strong laws, good enforcement, stiff sentences and a proper hospitalization programme are the necessary foundations upon which any successful programme must be predicated. These, plus an alert and determined public, will go a long way towards blotting out the problem. Probably the greatest reason for an increase in drug addiction has been the failure on the part of the legislators, of police, and of other officials to observe these important fundamentals. Most important, good results can be attained by perfecting the framework of the present federal and state laws, which are fundamentally sound.

Q. Considering the divergences in the approach to the problem of the addict, what measures would you suggest for the application of a law, for instance, of a state law, against narcotic offenders?

A. To make a law—such as New Jersey's—function, and to prevent any abuses, the following principles must be observed:

1. Addict violators who are placed on probation must be given a probationary period of at least five years. Control of the addict during the period of his treatment and rehabilitation is imperative;

2. The addict violator shall be required, as a condition of his probation, to submit to hospital treatment and to remain hospitalized until released by competent medical authority;

3. The addict violator shall be required, as a condition of his probation after discharge from the institution, to submit to a thorough examination each month by a public health doctor for the remainder of his probationary period. This is the only accurate way to determine whether or not an individual has commenced taking drugs again;

4. Probation authorities should be required to keep a very close check on drug violators after their discharge from the institution and to submit monthly reports to the court by which the individuals were sentenced;

5. A comprehensive program of follow-up care should be set up either by the state or local community with the co-operation of judges, doctors, probation and parole authorities and social welfare agencies. This is of vital importance since the lack

The Honourable Harry J. Anslinger

of follow-up care has been the greatest cause of recidivism;

6. Maximum sentences should be used against the professional criminal with no probation, parole, or suspension of sentence being granted in any case. The minimum sentence for the narcotic peddler should be five years. To escape the punishment he may lead law enforcement officers to the source of supply;

7. Bargain pleas made with the intent to lighten sentences should not be accepted by a prosecuting attorney;

8. Every case, no matter how small the amount of narcotics involved may be, shall be presented to the Grand Jury and vigorously prosecuted;

9. In any case involving a sale of narcotic drugs by an adult to a minor, the offender will receive the maximum sentence which the particular state or federal law allows.

Q. Do you think that teen-age addiction is a new and ominous phenomenon?

A. The addiction of persons in their late teens, loosely referred to as teen-age addiction, is not novel in this country. Heroin was used by this age group in the early 1900's. It was one of the developments which brought about the enactment of the Harrison Narcotic Law in 1914 and later on, other federal and state laws outlawing the narcotic traffic.

The following is cited from a report of a special committee appointed by the Secretary of the Treasury in 1919: "Most of the heroin addicts are comparatively young, a portion of them being boys and girls under the age of twenty. This is also true of cocaine addicts." But after the outbreak following the First World War, the tendency was for fewer young people to become addicted. The new addicts were in a slightly older category and the youthful addict became an exception and a curiosity.

On the basis of First World War experience, the Bureau of Narcotics feared and predicted some rise in addiction after the Second World War, and these forebodings proved to be well justified. An increase in addiction was noted around 1948, first as a trickle and then as a small stream. By 1952, admissions to federal narcotic hospitals and other factors showed that the crest of that increase had been passed. However, the situation remains a dangerous one, the correction of which is a challenge to the best efforts of everyone concerned.

It is the considered judgment of officials in the Bureau of Narcotics that this epidemic of narcotic addiction among younger people is primarily an extension of a wide-spread surge of juvenile delinquency. While it cannot be completely dismissed or completely described as a big-city problem, that, practically speaking, is the situation. Also, it is a problem confined for the most part to those areas where many factors contribute to delinquency and lawlessness among the affected youth.

Q. What do you think of the clinic plan in the cure of drug addiction?

A. The clinic plan recently advocated by a small minority group in one section of the country would radically change the present plan of enforcement and revert to dispensing narcotic drugs to drug addicts for the purpose of maintaining addiction. Under this plan anyone who is now or who later becomes a drug addict would apply to the clinic and receive the amount of narcotic drug sufficient to maintain his customary use. The proponents of the plan claim that the dope peddler would thus be put out of business.

William F. Tompkins

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This plan would elevate a most despicable trade to the avowed status of an honourable business, nay, to the status of practice of a time-honoured profession; and drug addicts would multiply unrestrained, to the irrevocable impairment of the moral fibre and physical welfare of the American people.

The answer to the problem is not, therefore, to accept narcotic drug addiction as a necessary evil and calmly proceed to ration with a daily supply each and every person who applies for the ration. It should rather be the provision by the states of facilities for scientific treatment of these unfortunates, looking toward a cure, coupled with vigorous and unremitting efforts toward elimination of improper sources of supply so as to facilitate complete rehabilitation of the reclaimed addict and prevent the addition of recruits to the ranks of these unfortunates. By scientific treatment is meant that professional treatment which includes confinement or restraint upon the addict to ensure that no surreptitious source of supply is available to him that would defeat the purpose of the attending physician.

Q. Would you say then that the addict cannot be cured?

A. Yes and no, depending on individual circumstances. Young people and those addicted a short time are the best prospects. There is at Lexington the finest hospital of its kind in the world. Many experts will cite an over-all rate of 25 per cent cures; cynics off the record will claim that it actually is no more than 2 per cent. At the best, these are harsh statistics. The bright side, however, is the Lexington story. From 1935 to 1952, 18,000 addicts were admitted for treatment. Of these, 64 per cent never returned for treatment, 21 per cent returned a second time, 6 per cent a third time, and 9 per cent four or more times.

One final word. Those who fight drug addiction are fighting uphill with the odds very much against them. There is no sure cure, no complete knowledge, and the chances of winning are definitely not too good. It may very well be the beginning of the end —a short and horrible existence. The best cure for addiction? Never let it happen!

TECHNICAL

The Physical Methods for the Identification of Narcotics

A series of articles, written under the direction of Charles G. Farmilo and Leo Levi

Organic Chemistry and Narcotic Section, Food and Drug Laboratories

Department of National Health and Welfare, Ottawa, Canada

PART IB[1]

The Common Physical Constants for Identification of Ninety-five Narcotics and Related Compounds

By Charles G. Farmilo, P. M. Oestreicher and Leo Levi, Organic Chemistry and Narcotic Section, Food and Drug Laboratories, Department of National Health and Welfare, Ottawa

The usual schemes of organic analysis referred to in part IA, table I (1),[2] include the determination of the common physical constants, boiling point, melting point, empirical formula, molecular weight, optical rotation, refractive index, etc. In order to authenticate narcotics for X-ray, ultra-violet, and infra-red examination, the melting or boiling points and water of crystallization were determined and the "wet" molecular weights caclulated. Elemental analysis and calculation of empirical formulas from C, H, N, and O values were not undertaken at this time. Most substances which were studied were commercial preparations and met official requirements.

The object of this paper is to review common physical constants of narcotics, to present methods of preparation of narcotic free bases, the results of water analyses, melting or boiling points, and acidity coefficients of ninety-five narcotics and related compounds. Empirical formulas, molecular weights and specific optical rotations obtained from the chemical literature were tabulated along with other data useful in identification.

Materials

The various narcotics and related compounds were originally obtained from the various sources, mainly commercial, shown in table I, column 2, at the end of this article. A number of free bases were prepared from the commercial salts and are indicated in table I, column 2, by a footnote. Commercial samples were otherwise used without further purification for the ultra-violet and infra-red studies, and for most of the X-ray work. Single crystals were grown in some cases for special X-ray studies by Dr. W. Barnes and details of these experiments are given in part IIB (2).

Names and nomenclature

The problem of selecting a name for each substance from the multiplicity of chemical, common, official, and trade names is one which had to be faced to simplify tabulation and discussion. Recently Kautz (3) and Miller (4) outlined the same problem in relation to views of various national and international organizations and reviewed some general rules arrived at by WHO for setting up non-proprietary names (5).

By no means all of the substances regarded as narcotics by the United Nations and the Canadian Narcotic Control Division, Department of National Health and Welfare, have been given official non-proprietary names. A comprehensive list of names for narcotics used in various manufacturing countries has been prepared by the Narcotic Division of the United Nations (33). The selection of one name is often difficult since as many as twenty names in the English language occur for some compounds. It is obvious that one name has to be given primacy in each case.

It was decided that since this work would be mostly used by chemists, expanded chemical and common chemical names would be employed in the main tables and for labelling the spectra of the narcotics.

The following rules for selecting names for narcotics were adhered to as far as possible.

1. The name was, if possible, selected from the following sources, so far as their decisions were known to us in the order of preference given:

[1] For part IA, see *Bulletin on Narcotics*, vol. V, No. 4.

[2] Figures in parentheses throughout the text refer to the numbered publications listed at the end of this article.

(*a*) International Pharmacopoeia and international non-proprietary names selected by the WHO Expert Committee on the International Pharmacopoeia;

(*b*) British Pharmacopoeia and approved non-proprietary names selected by the Pharmacopoeia Commission of the General Medical Council;

(*c*) United States Pharmacopeia and approved non-proprietary names selected by the Council on Pharmacy and Chemistry of the American Medical Association (these names are used in New and Non-Official Remedies);

(*d*) The Merck Index of Chemicals and Drugs.

2. The name was devised according to the rules of nomenclature for the international non-proprietary names (5).

3. Expanded chemical names were based on International Chemical Union rules of nomenclature given in Chemical Abstracts and The Ring Index (6). These names are also given in the Merck index (7).

One trade name, Acedicon ® (7) has been used as the only available brief name of the compound dihydrocodeinone enol acetate hydrochloride.

Common names and some trade names are listed in table II. The common or non-proprietary names are used for photographs, tables of data, and in discussion in the text. Following the common name in brackets, in table II, a chemical name is given, for example, *dl*-alphaprodine hydrochloride; (piperidine -1,3-dimethyl-4-phenyl-4-propionoxy hydrochloride (*dl*-α-(cis)). The name in parentheses is the form of the name used in table I. Normally, the chemical name would read *dl*-α-(cis)-1,3-dimethyl-4-phenyl-4-propionoxypiperidine, as used in indexing spectra. However, it is desirable to bring out chemical relationships in tables and the index style of Chemical Abstracts is preferred for this reason.

In table II, trade names that are registered in the United States Patent Office have a small letter ® to designate this fact. Others may be registered as trade names in other countries but, in the latter cases, no letter ® follows the name. In both cases the name is begun with a capital letter, when used in the ordinary text of subsequent articles, while the common names and the chemical names are uncapitalized.

Preparation of free bases of the narcotics

Samples (300 mg.) of the commercial hydrochlorides of ketobemidone, methylketobemidone, oxycodone, cocaine, hydromorphone, pethidine, and *d*-, *l*-, and *dl*-methadones, and racemorphan hydrobromide and dihydrocodeinone bitartrate were dissolved in a minimum volume of water (about 1 cc. in most cases) and the free bases precipitated with concentrated ammonium hydroxide; aqueous solutions of metopon, pipidone, ethylmorphine, isomethadone, and phenadoxone hydrochlorides were treated with 2N ammonium hydroxide; hydroxypethidine, alphaprodine, benzylmorphine, and diamorphine free bases were prepared from aqueous solutions of hydrochlorides by reaction with dilute sodium hydroxide. All the bases were obtained as solids except alphaprodine, pipidone, isomethadone, and pethidine, which separated from aqueous solutions as viscous oils. The mother liquors were removed from the solids by decanting and were filtered; the solids washed with cold water and recrystallized twice from 95 or 100 per cent ethanol, then dried in the presence of phosphorous anyhydride in a vacuum desiccator at reduced pressures. The solids were stored in the dark in small glass vials with plastic screw tops. In the case of the oils mentioned above, the base was dissolved in ether and the aqueous mother liquor extracted with ether. The combined ether extracts were dried in contact with Na_2SO_4 (anhydrous), then the volume of ether was partially reduced and the remaining ether solution poured into a Späth bulb, washed down with a small volume of clean, dry ether. The ether was completely removed at reduced pressure from the Späth bulb, carefully, by means of a water aspirator pump, and the oily residue distilled in an all-glass system at greatly reduced pressure (0.01—0.1 mm. Hg) by means of a mercury diffusion pump backed by a mechanical pump. The boiling point of the base was determined at this time; and the oil then removed from the distillation bulbs and run into vials which were sealed and stored in a refrigerator. The sample of pethidine oil, after refrigeration for about two weeks, solidified into a mass of needle-like crystals.

Methods of analysis

1. Melting points of the pure crystalline narcotic bases were determined, using a Fisher-Johns melting-point block. The rate of heating of the compound was noted.

Melting and boiling points of all the substances, salts and free bases, compared with values obtained from the chemical literature, are collected in table I for easy reference. Commercially available samples obtained from various drug companies were found to meet the required pharmacopoeial specifications of purity by quantitative analysis (9, 10), and were used without further treatment. Certain samples used without purification showed results which were different from the literature or expected values. The anomalies have been indicated by special notes on individual compounds in the experimental parts of the papers dealing with the individual methods, i.e., the X-ray, U.V., I.R., etc. This information will be useful in practical identification work.

2. Water of crystallization and free or adherent water were together determined by means of a modified Karl Fischer titration technique (11). The remaining compounds were dried in an Aberhalden pistol under reduced pressure to a constant weight. The weight difference was taken as loss of water. In some cases sublimation occurred at the pressure and temperatures used, and these cases are also noted.

3. The pK_A values of the substances (9) were determined by the fractional neutralization of salts according to the method given by Saunders and Srivastava (12).

4. Optical rotation values were not experimentally determined for this study but values given in the literature and references are given in table I.

Results

Physical data for the identification of narcotics and related compounds are listed in table I. The chemical name of the compound is listed in column 1. The source of the material is shown in column 2. Empirical formulas based on the generally accepted formula of the compound and the corresponding molecular weight are given in columns 3 and 4 respectively. The water content of the compounds as per cent and mole of water is shown in columns 5 and 6, along with the calculated molecular weight (computed by adding the found molecular weight of water to the anhydrous weight) is shown in column 7. Found and given melting points or boiling points are shown in columns 8 and 9 along with the literature reference in column 10. The specific optical rotation, and the concentration, solvent, and temperature used, and literature reference, are tabulated in columns 11 and 12. The acidic dissociation exponents, pK_A, determined previously (9) are tabulated in column 13.

Some notes on individual compounds are given in the following section. In table I, attention is called to them by a footnote.

Notes on individual compounds

Codeine (free base)

The sample described in table I must have contained a large number of prismatic crystals of the monohydrate. Over a period of time much of the sample appeared to have lost water of crystallization as shown by Karl Fischer determinations. The anhydrous material was used for both ultra-violet and infra-red studies. It should be noted for purposes of analysis that codeine monohydrate is efflorescent.

Codeine phosphate

The sample described in table I, employed for ultra-violet and infra-red examinations, was probably a mixture of hydrates. Codeine phosphate hydrates with 1, 1.5 and 2 moles of water have been reported (13) and the higher ones are said to be efflorescent (14). Variations in the water content of the samples submitted for X-ray diffraction have been noted by Barnes and Sheppard (2). The sample reported in table I was found to contain 1.22 moles water.

Codeinone, dihydro (free base) and codeinone, dihydrohydroxy (free base)

Water of crystallization was determined in both of these samples described in table I, using small amounts (5 mg.) of the free bases. Both were found to be anhydrous when dried at 55°C and 0.1 mm. Hg pressure using an Aberhalden drying pistol. Both also sublimed at 100°C and 0.1 mm. Hg.

Cotarnine (free base)

Two samples of cotarnine were available for study, the first (described in table I) was a dull brick red in color. The second, having similar common physical constants, was faint yellow in color. The color change is apparently a result of ageing. A careful study of the thermal and hydration reactions of cotarnine is required.

dl-3-Heptanone, 6-dimethylamino-4,4-diphenyl, HBr

Two samples of the methadone hydrobromide were available for analysis. The original commercial sample (B) was found to contain 0.048 moles of water, indicating the lack of water of crystallization. Subsequent analysis showed the commercial sample to contain some methadone HCl as an impurity. A sample of methadone hydrobromide (A) (free of hydrochloride) was prepared, which was used for further studies. X-ray diffraction showed the methadone hydrobromide portion of the sample (B) to be identical with the laboratory preparation (A). Both compounds B and A are described in table I.

dl-3-Hexanone, 6-diamethylamino-4,4-diphenyl-5-methyl (free base) and dl-3-hexanone, 6-piperidine-4,4-diphenyl-5-methyl (free base)

Both compounds were obtained as liquids and purified by distillation in a high vacuum. They were essentially anhydrous when prepared and were stored under anhydrous conditions.

Isoquinoline, 6,7-dimethoxy-1-veratryl, HCl

This sample of papaverine hydrochloride was dried in an Aberhalden drying pistol at 100°C and 0.1 mm. Hg for several days. No loss in weight was found. The sample was found to be anhydrous. Sublimation occurred at 140°C and 0.1 mm. Hg.

dl-Morphinan, 3-methoxy-N-methyl, HBr, monohydrate

The different melting ranges were observed when conditions of heating were altered. If a sample was placed on the block at 50°C (or lower) the melting range was observed to be 112°-115°C. When the sample was placed on the melting block which was heated to 75°-80°C, then complete melting of the sample was observed between 82° and 85°C. It was assumed that dehydration (loss of 1 mole of water) occurred when the sample was heated at a rate of 5°/min. from a temperature of 50° to 112°-115°C. No difficulties were encountered in determination of water of crystallization.

Morphine, HI, dihydrate

Three melting point ranges for morphine hydrogen iodide dihydrate were observed:

Block temp. °C	*Observed m.p. °C*
80-120	(*a*) 180-185
120-138	(*b*) 250-253
139	(*c*) 140-141

The sample melted in range (*a*) when the block temperature was initially between 80°-120°C. The true melt-

ing point of the dihydrate of morphine HI appears to be (*c*), 140°-141°C. The melt (*a*) recrystallizes at about 200°C and then melts again at 250°-253°C with decomposition.

Two samples of morphine HI were available for study. The first, sample A, was a commercial sample, the second, B, was prepared in our laboratory. They were identical in properties.

Morphine, H_2SO_4, dihydrate and pentahydrate

Three commercial preparations of morphine sulfate were titrated with Karl Fischer reagent and the averages of five titrations were obtained. The moles of water per mole of narcotic were 4.98, 5.14 and 5.14 respectively. It was observed by Barnes and Sheppard (2) that morphine sulfate pentahydrate was readily changed to a dihydrate on exposure to high temperatures and low humidity, conditions which sometimes exist in the laboratory.

Morphine, diacetyl, (free base) anhydrous

Water of crystallization was obtained by drying under reduced pressure in an Aberhalden drying pistol. The sample was anhydrous at 56°C and 1.0 mm. Hg and sublimed at 100°C and 1.0 mm. Hg.

Morphine, ethyl, HCl dihydrate

Two melting points were observed:

Block temp. °C	*Observed m.p. °C*
123	(*a*) 123
125 or less	(*b*) 150-160

No recrystallization phenomenon was observed.

Morphinone, dihydro (free base), anhydrous

A sample of dihydromorphinone free base was dried in the Aberhalden drying pistol over P_2O_5 and showed no weight loss after 12 hours at 70°C and 10 mm. Hg. The sample was assumed to be anhydrous.

Morphothebaine, HCl anhydrous

No loss of weight was observed when a sample of morphothebaine hydrochloride was heated at 155°C and 0.1 mm. Hg for 5 days in an Aberhalden drying pistol containing P_2O_5. The sample was assumed to be anhydrous.

Narceine (free base) and narceine hydrochloride

Narceine free base and narceine hydrochloride hydrates have been reported (7, 13) with 1 or 3, and 1, 3 or 5½ moles water per mole anhydrous free base and anhydrous salt respectively. Karl Fischer titration of commercial samples of the free base and salt indicated an average value of 1.72 mole and 0.26 mole water respectively. The melting points for narceine free base mono- and trihydrates are given as 138°C and 176°C respectively and the melting point found for the intermediate hydrate 152°-155°C. Melting point ranges of 188°-192°C and 192°-193°C have been reported by Merck (7) and Small (13) for anhydrous narceine hydrochloride. The observed melting point for the intermediate narceine hydrochloride hydrate (0.26 mole H_2O) was dependent upon the temperature of the block at the beginning of the melting point determination. If the material was placed on the block at 120°C, the observed melting point range was 148°-157°C, and if placed on the block before 120°C, the melting occurred at 190°C.

dl-α- (cis)-Piperidine, 1,3-dimethyl-4-phenyl-4-propionoxy

A sample was prepared from the anhydrous alphaprodine hydrochloride. It gave a boiling point of 70°-175°C at 0.02 mm. Hg and did not crystallize on further purification. Ziering (26) obtained a crystalline material melting 130°C.

dl-α-(cis)- and, dl-α-(trans),-Piperidine, 1,3-dimethyl-4-phenyl-4-propionoxy HCl

The samples of *dl*-alphaprodine and *dl*-betaprodine hydrochlorides were examined by Barnes and Sheppard (2) who separated crystals of two different habits from the anhedral fragments composing a large part of *dl*-betaprodine hydrochloride. Both crystal types were monoclinic but those of alphaprodine hydrochloride were pseudo-rectangular plates while those of betaprodine hydrochloride were pseudo-hexagonal plates. The alphaprodine hydrochloride sample was homogeneous and the betaprodine hydrochloride was non-homogeneous with respect to crystal type. Melting points given by Ziering (26) are 214°-215°C and 218°-220°C for alphaprodine hydrochloride, and 190°-192°C for betaprodine hydrochloride. The observed melting points were 223°-225°C using a heating rate of 1°/min. and 193°-194°C using a heating rate of 5°/min. for the alpha and beta compounds respectively. The samples of alpha and betaprodine hydrochloride were used for ultra-violet and infrared studies without further purification.

Piperidine, ethyl-1-methyl-4-phenyl-4-carboxylate (free base)

Two samples of pethidine (free base) were available, one laboratory preparation (A) and one commercial sample (B). Sample A, prepared from commercial pethidine hydrochloride was an oil which distilled at 80°-100°C at 0.025 mm. Hg. It yielded crystals on standing which, like those of sample B, melted at 31°-34°C using a heating rate of 2°/min. Bergel (27) reported pethidine (free base) to be a liquid boiling at 115°C at 0.2 mm. Hg.

Protopine (free base)

Three samples of protopine (free base) were available for examination. The original sample A contained two crystalline phases, one comprised of clear crystal fragments, the other a mass of fine powder. A water analysis on sample A indicated the material to be anhydrous. Sample B was obtained from the same commercial source as sample A, while sample C is an authentic sample of

protopine supplied by Dr. Leo Marion. Samples B and C were found by Barnes and Sheppard (2) to be homogeneous and identical. Sample A melted at 206°-208°C; samples B and C melted at 208°C and 209°C, respectively. Samples A and C were studied by means of ultraviolet and X-ray methods, and findings are discussed by Barnes and Sheppard (2) and by the present authors (8).

Samples A and C are described in table I. There appears to be a second component in sample A which is unidentified.

Pseudomorphine (free base)

Only a small amount of the pseudomorphine (free base) was available for experiments.

Karl Fischer titration indicated 3 moles of water were present; duplicate analyses were not made. The trihydrate form was assumed to be present.

Tropane, 3-hydroxy, carboxylic acid (ecgonine)

The sample of ecgonine was a commercial grade obtained from Merck and Co. It was a thick viscous liquid.

TABLE I. PHYSICAL DATA FOR NARCOTIC AUTHENTICATION

Compound Chemical name (Non-proprietary name)	Source	Empirical formula	Mol. wt.	Water analyses: Per cent	Water analyses: Moles	Water analyses: Mol. wt. used	Melting or boiling point: Found	Melting or boiling point: Given	Melting or boiling point: Ref.	Optical rotation: $[\alpha]^{t°}$ D given	Optical rotation: Ref.	Acid coefficient: pK_a found
apomorphine, HCl	T. & H. Smith	$C_{17}H_{17}NO_2.HCl.\frac{1}{2}H_2O$	312.8	3.88	0.68	316.04	225-236d. No m.p.	—	—	−48, c = 1.2, t = 25	7	7.17
benzoic acid, 5,6-dimethoxy-2-formyl (opianic acid)	T. & H. Smith	$C_{10}H_{10}O_5$	210.18	0.32	0.04	210.85	145.5-147 1°/min.	150	7 & 13	—	—	—
codeine	T. & H. Smith	$C_{18}H_{21}NO_3$	299.36	0.00**	0.00	299.36	154.5-156 3°/min.	155	—	monohydrate −136, p = 2, t = 15 alcohol −112, p = 2, t = 15 chloroform	7	—
codeine, H_3PO_4	T. & H. Smith	$C_{18}H_{21}NO_3.H_3PO_4.1\frac{1}{2}H_2O$	424.38	5.26**	1.22	419.40	233-236d. 5°/min.	dihydrate 235d	14	−134	14	8.22
codeine, dihydro	T. & H. Smith	$C_{18}H_{23}NO_3$	301.37	0.09	0.02	301.66	111.5-112 1°/min.	112-113	7	−145, c = 1.38 t = 20 ethanol	15	8.68
codeinone, dihydro (hydrocodone)	*	$C_{18}H_{21}NO_3$	299.36	0.00**	0.00	299.36	197-200 5°/min.	198	7 & 13	—	—	6.61
codeinone, dihydro, $C_4H_6O_6$ (hydrocodone bitartrate)	Knoll	$C_{18}H_{21}NO_3.C_4H_6O_6.2\frac{1}{2}H_2O$	494.47	8.35	2.27	490.34	119-125d. 5°/min.	146-148	7 & 13 7	—	—	—
codeinone, dihydro, enol acetate. HCl (acedicone® hydrochloride)	Boehringer	$C_{20}H_{23}NO_4.HCl$	377.85	4.15	0.91	394.19	226-245d. 5°/min.	132-135	7 & 13	—	—	—
codeinone, dihydrohydroxy (oxycodone)	*	$C_{18}H_{21}NO_4$	315.36	0.00**	0.00	315.36	224-225.5 5°/min.	218-220	7 & 13	—	—	—
codeinone, dihydro-hydroxy, HCl (oxycodone hydrochloride)	E. Merck	$C_{18}H_{21}NO_4.HCl$	351.82	5.82	1.21	373.55	242-250d. 1°/min.	268-270 anhydrous 270-272d.	13 7	anhydrous −125, c = 2.5, t = 20	—	—
cotarnine	T. & H. Smith	$C_{12}H_{13}NO_4$	237.25	6.14	0.86**	252.77	95-105d. 5°/min.	anhydrous 132-133d.	7	—	—	—
cryptopine	T. & H. Smith	$C_{21}H_{23}NO_5$	369.40	0.32	0.06	370.57	220-223d. 1°/min.	220-221	7	—	—	—
ecgonine, benzoyl, methyl (cocaine)	*	$C_{17}H_{21}NO_4$	303.35	0.39	0.07	304.54	96-98 5°/40 sec.	98	7	−35, c = 1, t = 18 50% ethanol −16, c = 4 t = 20 chloroform	7	—
ecgonine, benzoyl, methyl, HCl (cocaine hydrochloride)	Burroughs Wellcome	$C_{17}H_{21}NO_4.HCl$	339.81	0.27	0.05	340.74	177.5-180 1°/min.	195	7	−72, c = 2%, pH = 4.5	7	8.60
d-3-heptanone, 6-dimethylamino-4,4-diphenyl (*d*-methadone)	*	$C_{21}H_{27}NO$	309.44	0.25	0.04	310.16	98 5°/min.	100-101 99 98.7-99 98-100	16 17 18 19	+26, c = 1.5% t = 25, ethanol +29.51, c = 2.669, t = 26 absolute ethanol	16 18	— —
dl-3-heptanone, 6-dimethylamino-4,4-diphenyl (*dl*-methadone)	*	$C_{21}H_{27}NO$	309.44	0.05	0.01	309.60	74-80 5°/min.	78 79-81	7 16	—	—	—
l-3-heptanone, 6-dimethylamino-4,4-diphenyl	*	$C_{21}H_{27}NO$	309.44	0.12	0.02	309.80	98-99 5°/min.	100-101 99 93 7-99 99-101	16 7 & 17 18 19	−32, c = 1.8, t = 20 alcohol −26, c = 1.5%, t = 25 ethanol −29.91, c = 2.66 t = 22 absolute ethanol	7 16 18	— — —
dl-3-heptanone, 6-dimethylamino-4,4-diphenyl, HBr (*dl*-methadone hydrobromide)	*	$C_{21}H_{27}NO.HBr$	390.36	0.00**	—	390.36	—	—	—	—	—	—
	Shuttleworth	$C_{21}H_{27}NO.HBr$	390.36	0.22	0.05	391.24	228-231d. 5°/min.	—	—	—	—	—
d-3-heptanone, 6-dimethylamino-4,4-diphenyl, HCl (*d*-methadone hydrochloride)	Mallinckrodt	$C_{21}H_{27}NO.HCl$	345.90	0.25	0.05	346.78	225-246d. 5°/min.	243-244	16	+126, c = 1, t = 25 water +125, c = 1.5, t = 25 water +127.5, c = 2.96, t = 28, water	20 16 18	— — —

* Free base prepared from commercial salt.
** See Notes on Individual Compounds in preceding text.

TABLE I (*Cont'd—2*)

Compound Chemical name (Non-proprietary name)	Source	Empirical formula	Mol. wt.	Water analyses: Per cent	Water analyses: Moles	Water analyses: Mol. wt. used	Melting or boiling point: Found	Melting or boiling point: Given	Melting or boiling point: Ref.	Optical rotation: $[\alpha]^{t°}$ D given	Optical rotation: Ref.	Acid coefficient: pK_a found
dl-3-heptanone, 6-dimethylamino-4,4-diphenyl, HCl (*dl*-methadone hydrochloride)	Burroughs Wellcome	$C_{21}H_{27}NO.HCl$	345.90	0.10	0.02	346.23	230-249d. 5°/min.	235 229-230	7 16	—	—	8.25
l-3-heptanone, 6-dimethylamino-4,4-diphenyl, HCl (*l*-methadone hydrochloride)	Mallinckrodt	$C_{21}H_{27}NO.HCl$	345.90	0.23	0.04	346.71	237-247d. 5°/min.	241 245-246 241-242d.	7 16 19	−127.8,c=2.96 t=28,water −169,c=2.1 t=20,alcohol −127,c=1, t=25,water	18 7 20	—
dl-3-heptanone, 6-(N-morpholino)-4,4-diphenyl (phenadoxone)	*	$C_{23}H_{29}NO_2$	351.47	0.43	0.08	352.96	76-77 5°/45 sec.	75-76 75.5-77	7 32	—	—	—
dl-3-heptanone, 6-(N-morpholino)-4,4-diphenyl, HCl (phenadoxone hydrochloride)	Glaxo	$C_{23}H_{29}NO_2.HCl$	387.94	0.14	0.03	388.47	204-213d. 5°/min.	224-225d. 224-229	7 32	—	—	6.89 6.7 (25°C) 40% ethanol
d-α-3-heptanyl acetate, 6-dimethylamino-4,4-diphenyl, HCl (*d*-α-methadylacetate hydrochloride)	Merck	$C_{23}H_{31}NO_2.HCl$	389.95	2.26	0.50	398.98	211-214 5°/min.	215	7	+61.2,c=.02 t=25, ethanol-ether	7	
dl-α-3-heptanyl acetate, 6-dimethylamino-4,4-diphenyl, HCl (*dl*-α-methadylacetate hydrochloride)	Merck	$C_{23}H_{31}NO_2.HCl$	389.95	0.38	0.08	391.45	213-214 5°/min.	213-214	7	—	—	—
l-α-3-heptanyl acetate, 6-dimethylamino-4,4-diphenyl, HCl (*l*-α-methadylacetate hydrochloride)	Merck	$C_{23}H_{31}NO_2.HCl$	389.95	1.90	0.42	397.50	211-213 5°/min.	215	7	−60.c=.02, t=25, ethanol-ether	7	—
dl-3-hexanone, 6-dimethylamino-4,4-diphenyl-5-methyl (*dl*-isomethadone)	*	$C_{21}H_{27}NO$	309.44	0.00**	0.00	309.44	139 at 0.03 mm. Hg.	162-165 at 0.6 mm.Hg.	16	—	—	—
dl-3-hexanone, 6-dimethylamino-4,4-diphenyl-5-methyl, HCl (*dl*-isomethadone hydrochloride)	Mallinckrodt	$C_{21}H_{27}NO.HCl.H_2O$	363.91	4.70	0.95	362.95	130-135 5°/min.	153-155 145-149	16 21	—	—	8.07
dl-3-hexanone, 6-piperidino-4,4-diphenyl-5-methyl (pipidone)	*	$C_{24}H_{31}NO$	349.52	0.00**	0.00	349.52	135 at 0.03 mm. Hg.	—	—	—	—	—
dl-3-hexanone, 6-piperidino-4,4-diphenyl-5-methyl, HCl (pipidone hydrochloride)	Burroughs Wellcome	$C_{24}H_{31}NO.HCl$	386.00	0.18	0.04	386.7	189-196 5°/70 sec.	—	—	—	—	6.80
hydrastinine, Cl	(commercial)	$C_{11}H_{12}NO_2.Cl$	225.67	7.76	1.05	244.66	211-214 5°/min.	212d.	—	—	—	—
isoquinoline,6,7-dimethoxy-1-(4′-ethoxy-3′-methoxy-benzyl)-3-methyl,1½ H_3PO_4 (dioxyline phosphate)	Eli Lilly	$C_{22}H_{23}NO_4.1\frac{1}{2}H_3PO_4.\frac{1}{2}H_2O$	523.44	2.14	0.62	525.68	194-196 5°/min.	199-201	22	—	—	—
isoquinoline, 6,7-dimethoxy-l-veratryl (papaverine)	T. & H. Smith	$C_{20}H_{21}NO_4$	339.38	0.01	0.00	339.41	147-148 1°/min.	147	7	—	—	—

* Free base prepared from commercial salt.
** See Notes on Individual Compounds in the preceding text.

TABLE I (*Cont'd—3*)

Compound Chemical name (Non-proprietary name)	Source	Empirical formula	Mol. wt.	Water analyses: Per cent	Water analyses: Moles	Water analyses: Mol. wt. used	Melting or boiling point: Found	Melting or boiling point: Given	Melting or boiling point: Ref.	Optical rotation: $[\alpha]^{t°}$ D given	Optical rotation: Ref.	Acid coefficient: pK_a found
isoquinoline, 6,7-dimethoxy-l-veratryl, HCl (papaverine hydrochloride)	British Drug Houses	$C_{20}H_{21}NO_4.HCl$	375.84	0.00b	0.00	375.84	190-210d. 1°/min.	220-221 225-226	— 23	—	—	5.98
dl-laudanine	Späth's Collection	$C_{20}H_{25}NO_4$	343.40	0.00**	0.00	343.40	0.00b	166-167	7 & 13	—	—	—
dl-morphinan, 3-hydroxy-N-methyl (racemorphan)	*	$C_{17}H_{23}NO$	257.36	0.38	0.05	258.33	245-256 5°/min.	251-253	7	—	—	—
dl-morphinan, 3-hydroxy-N-methyl HBr (racemorphan hydrobromide)	Hoffmann-LaRoche	$C_{17}H_{23}NO.HBr.\frac{1}{2}H_2O$	347.29	2.64	0.51	347.47	186-192d. 1°/min.	193-195	7	—	—	8.97
l-morphinan, 3-hydroxy-N-methyl, $C_4H_6O_6$ (levorphan tartrate)	Hoffmann-LaRoche	$C_{17}H_{23}NO.C_4H_6O_6.2H_2O$	443.48	8.30	2.05	444.33	112-117 5°/min.	—	—	—	—	8.18
dl-morphinan, 3-methoxy-N-methyl (racemethorphan)	Hoffmann-LaRoche	$C_{18}H_{25}NO$	271.39	0.20	0.03	271.97	75-78 3°/min.	—	—	—	—	—
d-morphinan, 3-methoxy-N-methyl, HBr (dextromethorphan hydrobromide)	Hoffmann-LaRoche	$C_{18}H_{25}NO.HBr.H_2O$	370.32	5.02	1.03	370.93	112-117 5°/min.	—	—	—	—	—
dl-morphinan, 3-methoxy-N-methyl, HBr (racemethorphan hydrobromide)	Hoffmann-LaRoche	$C_{18}H_{25}NO.HBr.2H_2O$	388.34	9.57	2.07	389.58	82-85** 112-115 5°/min.	—	—	—	—	8.83
l-morphinan, 3-methoxy-N-methyl, HBr (levomethorphan hydrobromide)	Hoffmann-LaRoche	$C_{18}H_{25}NO.HBr.H_2O$	370.32	5.04	1.04	371.00	112-117 5°/min.	—	—	—	—	—
morphine	Merck	$C_{17}H_{19}NO_3.H_2O$	303.35	6.28	1.06	304.44	248.5-252d. 5°/min.	230d. rapid	7	monohydrate −132, c = 1, t = 25, methanol	7	9.85
morphine, HCl	Merck	$C_{17}H_{19}NO_3.HCl.3H_2O$	375.84	14.83	3.00	375.84	265-275d. 5°/min.	200	7 & 13	−111, c = 2.2%, t = 25, water −99.54, p = 1, t = 15	7 13	8.05
morphine, HI	Merck	$C_{17}H_{19}NO_3.HI.2H_2O$	449.29	8.07	2.01	449.51	140** 180-185 250-253d. 5°/min.	282d.	30	−115.8, water	30	—
morphine, H_2SO_4	Merck	$(C_{17}H_{19}NO_3)_2.H_2SO_4.5H_2O$	758.82	12.16	5.14	761.29	235-250d. 1°/min. no m.p.	anhydrous 250d. (app.)	—	−94.5, c = 4% t = 25, water −99.54, p = 1, t = 15	—	8.02
morphine, benzyl	*	$C_{24}H_{25}NO_3$	375.45	0.54	0.11	377.50	130.5-132.5 5°/min.	—	—	—	—	—
morphine, benzyl, HCl	T. & H. Smith	$C_{24}H_{25}NO_3.HCl$	411.91	0.52	0.12	414.05	205-235d. 1°/min.	233-236	30	−88.9, water	30	8.07
morphine, diacetyl (diamorphine)	*	$C_{21}H_{23}NO_5$	369.40	0.00**	0.00	369.40	168-173d. 5°/min.	173	13	−166, c = 1.49, t = 25, methanol	7	—
morphine, diacetyl, HCl (diamorphine hydrochloride)	T. & H. Smith	$C_{21}H_{23}NO_5.HCl.H_2O$	423.88	4.46	1.05	424.83	228-232 5°/40 sec.	231-232	13	−156, c = 1.044, t = 24	—	7.83
morphine, dihydro	T. & H. Smith	$C_{17}H_{21}NO_3.H_2O$	305.37	6.19	1.05	306.33	125-128d. 5°/min.	anhydrous 157d.	7	—	—	8.55
morphine, ethyl	*	$C_{19}H_{23}NO_3.H_2O$	331.40	6.71	1.25	335.92	60-63 5°/min.	93	7	—	—	—
morphine, ethyl, HCl	Mallinckrodt	$C_{19}H_{23}NO_3.HCl.2H_2O$	385.88	9.40	2.01	386.18	123d.** 150-160d. 1°/min.	123d. anhydrous 170d.	7 13	—	—	8.20
morphine, α-monoacetyl	N.Y., A.T.U. Lab.	$C_{19}H_{21}NO_4$	327.37	0.26	0.05	328.23	189-190.5 3°/min.	187	13	—	—	—

* Free base prepared from commercial salt.
** See Notes on Individual Compounds in the preceding text.

TABLE I (*Cont'd.*—4)

Compound Chemical name (Non-proprietary name)	Source	Empirical formula	Mol. wt.	Water analyses: Per cent	Water analyses: Moles	Water analyses: Mol. wt. used	Melting or boiling point: Found	Melting or boiling point: Given	Ref.	Optical rotation: $[\alpha]^{t°}$ D given	Ref.	Acid coefficient: pK_A found
morphine-N-oxide	T. & H. Smith	$C_{17}H_{19}NO_4$	301.33	0.57	0.10	303.06	245-270d. 1°/25 sec., no m.p.	274-275	7	—	—	4.82
morphinone, dihydro (hydromorphone)	*	$C_{17}H_{19}NO_3$	285.33	0.00**	0.00	285.33	266-270d. 5°/min.	265-267d. (evacuated tube)	7	−194, c=98, t=25, dioxane	4	—
*morphinone, dihydro, HCl (hydromorphone hydrochloride)	Knoll	$C_{17}H_{19}NO_3.HCl$	321.79	0.34	0.06	322.91	280-295d. 1°/min.	305-315d. (evacuated tube)	7	−133, c=1, t=25	7	8.15
morphinone, methyl, dihydro (hydromorphone hydrochloride)	*	$C_{18}H_{21}NO_3$	299.36	10.12	1.87	333.05	235-240d. 5°/45 sec.	235 sinters 243-245 melts (evacuated tube)	7	−141, c=1, t=24 alcohol	7	—
morphinone, methyl, dihydro, HCl (metopon hydrochloride)	Parke, Davis	$C_{18}H_{21}NO_3.HCl$	335.82	0.19	0.04	336.47	above 310	315-318d. (evacuated tube)	7	−105, c=1, t=24, alcohol	7	8.08
morphothebaine, HCl	Fulton	$C_{18}H_{19}NO_3.HCl$	333.80	0.00**	0.00	333.80	d. from 190 no m.p. by 300	256-260	7 & 13	—	—	—
narceine	T. & H. Smith	$C_{23}H_{27}NO_8$	445.45	6.50**	1.72	476.44	152-155d. 5°/min.	anhydrous 138 trihydrate 176	7	—	13	3.76
narceine, HCl	Merck	$C_{23}H_{27}NO_8.HCl$	481.92	0.85	0.25	486.05	148-157** 190 1°/min.	anhydrous 192-193 188-192	7 13	—	—	—
narceine, ethyl, HCl	T. & H. Smith	$C_{25}H_{31}NO_8.HCl$	509.97	0.65	0.18	513.30	203-204d. 5°/min.	208-210	7			8.04
narcotine	T. & H. Smith	$C_{22}H_{23}NO_7$	413.41	0.05	0.01	413.63	174-175 2½°/min.	176	7	−185, p=0.7, t=23, 97% alcohol	7	—
										−207, p=2, t=23, chloroform	7	—
narcotine, HCl	British Drug House	$C_{22}H_{23}NO_7.HCl.\frac{1}{2}H_2O$	458.88	2.43	0.63	461.10	174-178d. 1°/min.					6.24
neopine, HBr	Mallinckrodt	$C_{18}H_{21}NO_3.HBr$	380.28	0.04	0.01	380.42	292-296d. 5°/min.	240 darkens 282-283d. melts	7 & 13	+17.32, c=3.696, t=23, water	13	—
normorphine, N-allyl, HCl (nalorphine hydrochloride)	Merck	$C_{19}H_{21}NO_3.HCl$	347.83	0.29	0.06	348.85	242-243d. 1°/min.	269d.	7	—	—	7.83
P,β-phenethylamine, 3,4,5-trimethoxy, H_2SO_4 (mescaline sulfate)	Hoffmann-LaRoche	$(C_{11}H_{17}NO_3)_2.H_2SO_4.2H_2O$	556.61	6.66	2.06	557.74	186-189 5°/min.	183-186	7	—	—	—
β-phenethylamine, 3,4,5-trimethoxy-N-dimethyl, HCl (trichocereine hydrochloride)	Castrillon	$C_{13}H_{21}NO_3.HCl$	275.77	0.38	0.06	276.82	203-206 5°/min.	205	25	—	—	—
dl-α-(cis)-piperidine, 1,3-dimethyl-4-phenyl-4-propionoxy (Alphaprodine)	*	$C_{14}H_{22}NO_2$	261.35	0.00	0.00	261.35	70-75 at 0.02 mm. Hg.	**103	26	—	—	—
dl-α-(cis)-piperidine, 1,3-dimethyl-4-phenyl-4-propionoxy, HCl (*dl*-alphaprodine hydrochloride)	Hoffmann-LaRoche	$C_{14}H_{22}NO_2.HCl$	297.82	0.13	0.02	298.22	223-225** 1°/min.	214-215 218-220	7 26	—	—	8.73
dl-β-(trans)-piperidine, 1,3-dimethyl-4-phenyl-4-propionoxy, HCl (*dl*-betaprodine hydrochloride)	Hoffmann-LaRoche	$C_{14}H_{22}NO_2.HCl$	297.82	0.34	0.06	299.02	193-194** 5°/min.	190-192	26	—	—	—

* Free base prepared from commercial salt.
** See Notes on Invididual Compounds in the preceding text.

TABLE I (*Cont'd.*—5)

Compound Chemical name (Non-proprietary name)	Source	Empirical formula	Mol. wt.	Water analyses: Per cent	Water analyses: Moles	Water analyses: Mol. wt. used	Melting or boiling point: Found	Melting or boiling point: Given	Melting or boiling point: Ref.	Optical rotation: $[\alpha]^{25}$ D given	Optical rotation: Ref.	Acid coefficient: pK_a found
piperidine, ethyl-1-methyl-4-phenyl-4-carboxylate (pethidine)	*	$C_{15}H_{21}NO_2$	247.32	0.00	0.00	247.32	80-100** at 0.02 mm.	115 at 0.2 mm.	27	—	—	—
	Winthrop Stearns	$C_{15}H_{21}NO_2$	247.32	0.00	0.00	247.32	31-34** 2°/min.					
piperidine, ethyl-1-methyl-4-phenyl-4-carboxylate, HCl (pethidine-hydrochloride)	Winthrop Stearns	$C_{15}H_{21}NO_2.HCl$	283.79	0.17	0.03	284.27	186.5-188 1°/min.	186-189 187-189	7 27	—	—	8.72
dl-piperidine, ethyl-1-methyl-3-ethyl-4-phenyl-4-carboxylate, HCl (ethylpethidine hydrochloride)	Hoffmann-LaRoche	$C_{17}H_{25}NO_2.HCl$	311.84	0.15	0.03	312.32	236-239 5°/min.	—	—	—	—	—
piperidine, ethyl-1-methyl-4-(m-hydroxy-phenyl)-4-carboxylate, (hydroxypethidine)	*	$C_{15}H_{21}NO_3$	263.33	0.07	0.01	263.51	111-112 5°/min.	—	—	—	—	—
piperidine, ethyl-1-methyl-4-(m-hydroxy-phenyl)-4-carboxylate, HCl (hydroxypethidine hydrochloride)	Ciba	$C_{15}H_{21}NO_3.HCl$	299.79	0.18	0.03	300.32	174-177 1°/min.	—	—	—	—	8.62
4-piperidyl ethyl ketone, 4-(m-acetoxy-phenyl)-1-methyl, HCl (acetoxyketo-bemidone hydrochloride)	Ciba	$C_{17}H_{23}NO_3.HCl$	325.84	0.10	0.02	326.15	170-173 1°/min.	172-173	28	—	—	8.75
4-piperidyl ethyl ketone, 4-(m-hydroxy-phenyl)-1-methyl (ketobemidone)	*	$C_{14}H_{21}NO_2$	247.33	0.09	0.01	247.56	157-159 5°/min. U. V. sample	155-156	28	—	—	—
	*	$C_{14}H_{21}NO_2$	247.33	0.00	0.00	247.33	151-159 5°/min. X-ray sample	155-156	28	—	—	—
4-piperidyl ethyl ketone, 4-(m-hydroxy-phenyl)-1-methyl, HCl (ketobemidone hydrochloride)	Ciba	$C_{14}H_{21}NO_2.HCl$	283.79	0.21	0.03	284.40	202-203 1°/min.	201-202	28	—	—	8.67
4-piperidyl methyl ketone, 4-(m-hydroxy-phenyl)-1-methyl (methyl-ketobemidone)	*	$C_{14}H_{19}NO_2$	233.30	0.28	0.04	233.95	176-180 5°/min.	154-156	28	—	—	—
4-piperidyl methyl ketone, 4-(m-hydroxy-phenyl)-1-methyl, HCl (methylketo-bemidone hydrochloride)	Ciba	$C_{14}H_{19}NO_2.HCl$	269.76	0.19	0.02	270.21	218-220d. 1°/min.	—	—	—	—	8.61
4-piperidyl propyl ketone, 4-(m-hydroxy-phenyl)-1-methyl (propyl-ketobemidone)	Ciba	$C_{16}H_{23}NO_2$	261.86	0.16	0.02	261.79	158-159 1°/min.	153-154	28	—	—	8.62
protopine	Eastman Kodak	$C_{20}H_{19}NO_5$	353.36	0.00	0.00	353.36	206-208** 5°/min.	208	7 & 13	—	—	—
	Marion	$C_{20}H_{19}NO_5$	353.36	0.00	0.00	353.36	209**		29	—	—	—
pseudomorphine	Fulton	$C_{34}H_{36}N_2O_6.3H_2O$	622.69	**	—	622.69	Above 300d. 3°/min.	327d.	7	—	—	—

* Free base prepared from commercial salt.
** See Notes on Individual Compounds in the preceding text.

TABLE I (*Cont'd.—6*)

Compound Chemical name (Non-proprietary name)	Source	Empirical formula	Mol. wt.	Water analyses: Per cent	Water analyses: Moles	Water analyses: Mol. wt. used	Melting or boiling point: Found	Melting or boiling point: Given	Melting or boiling point: Ref.	Optical rotation: $[\alpha]^{25}$ D given	Optical rotation: Ref.	Acid coefficient: pK_a found
pyran, 1-hydroxy-3-n-hexyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzo (pyrahexyl ®)	Abbott	$C_{22}H_{32}O_2$	328.48	0.53	0.10	330.24	—	190-192 at 1 mm.	31	—	—	—
1,4-pyran, 3-hydroxy-4-oxo-2,6-dicarboxylic acid (meconic acid)	T. & H. Smith	$C_7H_4O_7.3H_2O$	254.08	20.21	2.81	250.76	285-290d. 5°/min. No m.p.	anhydrous 100-102 d.(CO_2)	7	—	—	—
sinomenine, HCl	Japan	$C_{19}H_{23}NO_4.HCl.2H_2O$	401.88	9.25	2.07	403.16	226-231d. 5°/min.	anhydrous 231d.	7	−82,c=4.4, t=17	7	
thebaine	T. & H. Smith	$C_{19}H_{21}NO_3$	311.37	0.05	0.01	311.54	191-193d. 1°/min.	192.5 193	13 7	−229,5,p=5, t=22.5 chloroform	13	8.15
										−218.64,p=2, t=15, 95% ethanol	13	—
thebaine, HCl	T. & H. Smith	$C_{19}H_{21}NO_3.HCl.H_2O$	365.85	0.00	0.00	365.85	190-199d. 8°/min.			−163.6,p=2, t=22.5 water	13	—
										−168.32	14	—
thebenine, HCl	Fulton	$C_{18}H_{19}NO_3.HCl.H_2O$	351.82	5.28	1.03	352.41	218-220 5°/min.	sinters 231 melts 235	13		—	—
2-tropane, 3-hydroxy, carboxylic acid (ecgonine)	Merck	$C_9H_{15}NO_3$	185.22	0.00**	0.00	185.22		monohydrate 198 anhydrous 205d.	7	monohydrate −45,c=5, t=15	7	monohydrate 11.11

* Free base prepared from commercial salt.
** See Notes on Individual Compounds in the preceding text.

TABLE II

LIST OF THE COMMON OR NON-PROPRIETARY NAMES USED, AND SOME OF THE BEST-KNOWN TRADE NAMES, WITH THE CORRESPONDING CHEMICAL NAMES

Acedicon® hydrochloride (codeinone, dihydro enol acetate, HCl)
Acetoxyketobemidone hydrochloride (4-piperidyl ethyl ketone,-4-(m-acetoxyphenyl)-1-methyl, HCl)
d-α-Acetyl methadol hydrochloride (see *d*-α-methadyl acetate hydrochloride)
dl-α-Acetyl methadol hydrochloride (see *dl*-α-methadyl acetate hydrochloride)
l-α-Acetyl methadol hydrochloride (see *l*-α-methadyl acetate hydrochloride)
dl-Alphaprodine (free base) (piperidine, 1,3-dimethyl-4-phenyl-4-propionoxy) (*dl*-α-(cis)
dl-Alphaprodine hydrochloride piperidine, 1,3-dimethyl-4-phenyl-4-propionoxy, HCl) (*dl*-α-(cis))
d-Amidone (free base) (see *d*-methadone (free base))
dl-Amidone (free base) (see *dl*-methadone (free base))
l-Amidone (free base) (see *l*-methadone (free base))
dl-Amidone hydrobromide (see *dl*-methadone hydrobromide)
d-Amidone hydrochloride (see *d*-methadone hydrochloride)
dl-Amidone hydrochloride (see *dl*-methadone hydrochloride)
l-Amidone hydrochloride (see *l*-methadone hydrochloride)
Apomorphine hydrochloride
Bemidone (free base) (see hydroxypethidine (free base))
Bemidone hydrochloride (see hydroxypethidine hydrochloride)
Benzylmorphine (free base) (morphine, benzyl)
Benzylmorphine hydrochloride (morphine, benzyl, HCl)
dl-Betaprodine hydrochloride (piperidine, 1,3-dimethyl-4-phenyl-4-propionoxy, HCl) (*dl*-β-(trans))
Cliradon® (free base) (see ketobemidone (free base))
Cliradon® hydrochloride (see ketobemidone hydrochloride)
Cocaine (free base) (ecgonine, benzoyl, methyl)
Cocaine hydrochloride (ecgonine, benzoyl, methyl, HCl)
Codeine (anhydrous free base)
Codeine monohydrate (free base)
Codeine phosphate (anhydrous)
Codeine phosphate dihydrate
Cotarnine (free base)
Cryptopine (free base)
Demerol® (free base) (see pethidine (free base))
Demerol® hydrochloride (see pethidine hydrochloride)
Dextromethorphan hydrobromide monohydrate (*d*-morphinan, 3-methoxy-N-methyl, HBr)
Diamorphine (free base) (morphine, diacetyl)
Diamorphine hydrochloride monohydrate (morphine, diacetyl, HCl)
Dicodid® (free base) (see dihydrocodeinone (free base))
Dicodid® bitartrate (see dihydrocodeinone bitartrate (dihydrate))
Dihydrocodeine (free base) (codeine, dihydro)
Dihydrocodeinone (free base) (see hydrocodone (free base)
Dihydrocodeinone bitartrate (see hydrocodone bitartrate (dihydrate))
Dihydromorphine monohydrate (free base) (morphine, dihydro)
Dihydromorphinone (free base) (see hydromorphone (free base))
Dihydromorphinone hydrochloride (see hydromorphone hydrochloride)
Dilaudid® (free base) (see hydromorphone (free base))
Dilaudid® (free base) hydrochloride (see hydromorphone hydrochloride)

Dionin (free base) (see ethylmorphine (free base))
Dionin hydrochloride (see ethylmorphine hydrochloride)
Dioxyline phosphate (isoquinoline, 6,7-dimethoxy-1-(4'-ethoxy-3'-methoxybenzyl)-3-methyl, 1-½ H_3PO_4)
Dolantin (free base) (see pethidine (free base))
Dolantin hydrochloride (see pethidine hydrochloride)
Dolophine® (free base) (see *dl*-methadone (free base))
Dolophine® hydrochloride (see *dl*-methadone hydrochloride)
Dromoran® (free base) (see racemorphan (free base))
Dromoran® hydrobromide (see racemorphan hydrobromide)
l-Dromoran® tartrate (see levorphan tartrate dihydrate)
Ecgonine (free base) (2-tropane, 3 hydroxy, carboxylic acid)
Ethylmorphine (free base) (morphine, ethyl)
Ethylmorphine hydrochloride (morphine, ethyl, HCl)
Ethylnarceine hydrochloride (narceine, ethyl, HCl)
Ethylpethidine hydrochloride (*dl*-piperidine, ethyl-1-methyl-3-ethyl-4-phenyl-4-carboxylate, HCl)
Eukodal® (free base) (see oxycodone (free base))
Eukodal® hydrochloride (oxycodone hydrochloride)
Genomorphine (see morphine-N-oxide)
Heptalgine® (free base) (see phenadoxone (free base))
Heptalgin® hydrochloride (see phenadoxone hydrochloride)
Heroin (free base) (see diamorphine (free base))
Heroin hydrochloride (see diamorphine hydrochloride monohydrate)
Hycodan® (free base) (see dihydrocodeinone (free base))
Hycodan® bitartrate (see dihydrocodeinone bitartrate (dihydrate))
Hydrastinine (hydro)chloride monohydrate
Hydrocodone (free base) (see codeinone, dihydro)
Hydrocodone bitartrate (codeinone, dihydro, $C_4H_6O_6$)
Hydromorphone (free base) (morphinone, dihydro)
Hydromorphone hydrochloride (morphinone, dihydro, HCl)
Hydroxypethidine (free base) (piperidine, ethyl-1-methyl-4-(m-hydroxyphenyl)-4-carboxylate)
Hydroxypethidine hydrochloride (piperidine, ethyl-1-methyl-4-(m-hydroxyphenyl)-4-carboxylate, HCl)
dl-Isoamidone (free base) (see *dl*-isomethadone (free base))
dl-Isoamidone hydrochloride (see *dl*-isomethadone hydrochloride monohydrate)
dl-Isomethadone (free base) (*dl*-3-hexanone, 6-dimethylamino-4,4-diphenyl-5-methyl)
dl-Isomethadone hydrochloride monohydrate (*dl*-3-hexanone-6-dimethylamino-4,4-diphenyl-5-methyl, HCl)
Ketobemidone (free base) (4-piperidyl ethyl ketone, 4-(m-hydroxyphenyl)-1-methyl)
Ketobemidone hydrochloride (4-piperidyl ethyl ketone, 4-(m-hydroxyphenyl)-1-methyl, HCl)
Levomethorphan hydrobromide monohydrate (*l*-morphinan, 3-methoxy-N-methyl, HBr)
Levorphan tartrate dihydrate (*l*-morphinan, 3-hydroxy-N-methyl, $C_4H_6O_6$)
dl-Laudanine (free base)
Meconic acid trihydrate (1,4-pyran, 3-hydroxy-4-oxo-2,6-dicarboxylic acid)
Meperidine (free base) (see pethidine (free base))
Meperidine hydrochloride (see pethidine hydrochloride)
Mescaline sulphate dihydrate (β-phenethylamine, 3,4,5-trimethoxy, H_2SO_4)
d-Methadone (free base) (*d*-3-heptanone, 6-dimethylamino-4,4-diphenyl)
dl-Methadone (free base) (*dl*-3-heptanone, 6-dimethylamino-4,4-diphenyl)
l-Methadone (free base) (*l*-3-heptanone, 6-dimethylamino-4,4-diphenyl)
dl-Methadone hydrobromide (*dl*-3-heptanone, 6-dimethylamino-4,4-diphenyl, HBr)
d-Methadone hydrochloride (*d*-3-heptanone, 6-dimethylamino-4,4-diphenyl, HCl)
dl-Methadone hydrochloride (*dl*-3-heptanone, 6-dimethylamino-4,4-diphenyl, HCl.
l-Methadone hydrochloride (*l*-3-heptanone, 6-dimethylamino-4,4-diphenyl, HCl)
d-α-Methadyl acetate hydrochloride (*d*-α-3-heptanyl acetate, 6-dimethylamino-4,4-diphenyl, HCl)
dl-α-Methadyl acetate hydrochloride (*dl*-α-3-heptanyl acetate, 6-dimethylamino-4,4-diphenyl, HCl)
l-α-Methadyl acetate hydrochloride (*l*-α-3-heptanyl acetate, 6-dimethylamino-4,4-diphenyl, HCl)
dl-Methorphan (free base) (see racemethorphan (free base))
d-Methorphan hydrobromide (see dextromethorphan hydrobromide monohydrate)
l-Methorphan hydrobromide (see levomethorphan hydrobromide monohydrate)
dl-Methorphan hydrobromide (see racemethorphan hydrobromide dihydrate)
dl-Methorphinan (free base) (see racemorphan (free base))
dl-Methorphinan hydrobromide (see racemorphan hydrobromide)
l-Methorphinan tartrate (see levorphan tartrate dihydrate)
Methylketobemidone (free base) (4-piperidyl methyl ketone-4-(m-hydroxyphenyl)-1-methyl)
Methylketobemidone hydrochloride (4-piperidyl methyl ketone-4-(m-hydroxyphenyl)-1-methyl, HCl)
Metopon (dihydrate) (free base) (morphinone, methyl, dihydro)
Metopon hydrochloride (morphinone, methyl, dihydro, HCl)
α-Monoacetylmorphine (free base) (morphine, α-monoacetyl)
Morphine hydriodide dihydrate
Morphine hydrochloride (anhydrous)
Morphine hydrochloride trihydrate
Morphine monohydrate (free base)
Morphine-N-oxide
Morphine sulphate dihydrate
Morphine sulphate pentahydrate
Morphine tartrate monohydrate
Morphothebaine hydrochloride
Nalorphine hydrochloride (normorphine, N-allyl, HCl)
Narceine (free base)
Narceine hydrochloride
Narcotine (free base)
Narcotine hydrochloride
Neopine hydrobromide
Nisentil® (free base) (see *dl*-alphaprodine (free base))
Nisentil® hydrochloride (see *dl*-alphaprodine hydrochloride)
β-Nisentil® hydrochloride (see *dl*-betaprodine hydrochloride)
Opianic acid (benzoic acid, 5,6-dimethoxy-2-formyl)
Oxycodone (free base) (codeinone, dihydrohydroxy)
Oxycodone hydrochloride (codeinone, dihydrohydroxy, HCl)
Papaverine (free base) (isoquinoline, 6,7-dimethoxy-1-veratryl)
Papaverine hydrochloride (isoquinoline, 6,7-dimethoxy-1-veratryl, HCl)
Paracodin® (free base) (see dihydrocodeine (free base))
Parahexyl (see pyrahexyl®)
Paveril® phosphate (see dioxyline phosphate)
Peronin (free base) (see benzylmorphine (free base))
Peronin hydrochloride (see benzylmorphine hydrochloride)
Pethidine (free base) (piperidine, ethyl-1-methyl-4-phenyl-4-carboxylate)
Pethidine hydrochloride (piperidine, ethyl-1-methyl-4-phenyl-4-carboxylate, HCl)
Phenadoxone (free base) (3-heptanone, 6-(N-morpholino)-4,4-diphenyl)
Phenadoxone hydrochloride (3-heptanone, 6-(N-morpholino)-4,4-diphenyl, HCl)
Physeptone (free base) (see *dl*-methadone (free base))
Physeptone hydrochloride (see *dl*-methadone hydrochloride)
Pipidone (free base) (3-hexanone,6-piperidino-4,4-diphenyl-5-methyl)
Pipidone hydrochloride (3-hexanone,6-piperidino-4,4-diphenyl-5-methyl, HCl)
dl-α-Prodine (free base) (see *dl*-alphaprodine (free base))
dl-α-Prodine hydrochloride (see *dl*-alphaprodine hydrochloride)
dl-β-Prodine hydrochloride (see *dl*-betaprodine hydrochloride)
Propylketabemidone (free base) (4-piperidyl propyl ketone, 4-(m-hydroxyphenyl)-1-methyl)
Protopine (free base)
Pseudomorphine trihydrate (free base)
Pyrahexyl® (pyran,1-hydroxy,3-n-hexyl,6,6,9-trimethyl,7,8,9,10-tetrahydro-6-dibenzo)

Racemethorphan (free base) (*dl*-morphinan, 3-methoxy-N-methyl)
Racemethorphan hydrobromide dihydrate (*dl*-morphinan, 3-methoxy-N-methyl, HBr)
Racemorphan (free base) *dl*-morphinan, 3-hydroxy-N-methyl)
Racemorphan hydrobromide (*dl*-morphinan, 3-hydroxy-N-methyl, HBr)
Sinomenine hydrochloride dihydrate
Synhexyl (see pyrahexyl®)
Thebaine (free base)
Thebaine hydrochloride
Thebenine hydrochloride monohydrate
Trichocereine hydrochloride (β-phenethylamine, 3,4,5-trimethoxy-N-dimethyl, HCl)

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PART IIA

The X-ray diffraction method on powder

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Introduction

The identification of crystalline materials by X-ray diffraction methods is a routine procedure in many laboratories. Its importance in the field of narcotics, however, does not appear to have received the general recognition that it deserves. Gross and Oberst (5)[1] have published X-ray diffraction data for fourteen substances, including hydrates, and Hubach and Jones (9) have studied *dl*-methadon-hydrochloride, but corresponding information on a large number of other narcotics is not available, at least in the literature.

The object of the present paper is to outline such basic principles of the interaction of X-radiation and crystalline matter as are necessary for an appreciation of the X-ray diffraction method as applied particularly to the identification of narcotics in the form of crystalline powders. The data required and the means for obtaining them are discussed briefly, and the power and limitations of the method are considered. X-ray diffraction powder patterns and tabulated numerical data for eighty-three narcotics are presented in a separate paper.

Equipment and techniques peculiar to the determination of the detailed structure of single crystals are not included in the present review although data collected by these means may also be used for identification purposes. No systematic scheme of identification based on single-crystal data, and comparable to that available for powdered materials, however, has been published although there is reason to believe that one may appear in the near future. In any case, many samples of narcotics, as normally received, do not contain crystals suitable for single-crystal measurements. Furthermore, the collection of the minimum X-ray diffraction data for the identification of a substance in the form of a single crystal frequently requires more time than is necessary when the same material is in finely powdered form.

For those who may wish to obtain more information on the X-ray diffraction powder method of identification, or who may wish to explore the use of data obtained from single crystals, a few references (2, 6, 8, 10, 15) are given. No attempt has been made to compile an extensive bibliography but further references may be obtained from those cited.

[1] Figures in parentheses throughout the text refer to the numbered publications listed at the end of this article.

Production and properties of X-radiation

X-radiation is produced whenever rapidly moving electrons impinge on matter. An X-ray tube consists essentially of an evacuated glass envelope containing two electrodes (anode, positive; cathode, negative) across which a high potential may be applied. Electrons are accelerated by the action of the electric field and are driven against the positive electrode (anode, anticathode, target) where the rapid reduction in their velocity results in the emission of X-radiation comprising all wave-lengths above a minimum value which corresponds to the instantaneous stopping of an electron moving with maximum possible velocity under the applied potential. The intensity of this continuous (or "white") radiation rises rapidly from zero, at the minimum wave-length, to a maximum and then decreases more slowly for increasing wave-lengths. As the voltage across the X-ray tube is increased, the minimum wave-length alters to lower values as does that for which the intensity is a maximum. At the same time the magnitude of the intensity at all wave-lengths increases. The wave-lengths comprising the continuous radiation, therefore, are independent of the target material, while the value of the minimum wave-length and the relative intensity at each wave-length above the minimum are governed by the applied potential.

Superimposed on the continuous radiation are intense rays of definite wave-lengths characteristic of the particular metal of which the target is composed. These characteristic X-rays arise from the disturbance of certain specific electrons in the atoms of the target material. The electrons outside the nucleus of an atom are classified in groups (shells, orbits; K, L, M, etc.) according to the amounts of energy required to remove them from the atom. X-rays of definite, characteristic wave-lengths are emitted when electrons from other groups (in higher energy levels) replace those of a given shell that have received sufficient energy to escape. Thus the Kβ line is emitted during the transition of electrons from the M to K shell while two lines (Kα_2, Kα_1) are produced by the transition of two electrons, with slightly different energies, from L to K shell. The excitation energy to remove electrons from a given shell is supplied by the electron beam in the X-ray tube. Since this energy must have a definite minimum value depending on the particular shell and the particular kind of atom involved, the characteristic X-rays are obtained only above a minimum

applied potential and they emerge with definite wave-lengths, both features being dependent on the specific chemical element making up the target. Thus the K lines of the X-ray spectrum of copper are emitted by an X-ray tube only if the potential is 9 kilovolts (kV) or more, while 20 kV is required to excite the K lines of molybdenum, and the wave-lengths of the Kβ, Kα_1, Kα_2 X-rays from copper are not the same as those of the corresponding rays from molybdenum.

The supply of electrons in the X-ray tube usually is furnished by a tungsten wire (filament) heated to incandescence and situated at the cathode. "Sealed-off" tubes, as their name implies, are permanently closed at the factory after evacuation, while "continuously pumped" or "demountable" tubes depend on the operation of a pumping system to maintain a satisfactorily low pressure during operation. The first type is generally more popular in North America while the second is frequently used in Great Britain and on the European continent. During operation of either type, tungsten distills slowly from the hot filament and condenses on the target and on the windows through which the X-rays emerge from the tube; eventually the filament breaks. The deposit on the target gives rise to X-radiation characteristic of tungsten superimposed on that of the target metal. Under certain conditions the interpretation of diffraction patterns may be complicated by this feature. The formation of a thin film of tungsten over the windows of the tube tends to decrease their transmission for X-radiation and hence reduces the intensity of the X-ray beam obtainable under a given set of operating conditions. A demountable tube, however, can be taken apart in the laboratory for cleaning, for interchanging targets of different metals, and for replacing burned-out filaments. Thus the purity of radiation can be maintained and only one X-ray tube, with spare targets of different metals and a supply of filaments, is required for all purposes. On the other hand, an X-ray unit with sealed tubes generally requires much less maintenance. Capital expenditure is higher because a complete tube is required for each target material and must be replaced when the filament burns out or if the tube becomes "gassy" (i.e., if the pressure in the tube rises appreciably). Nevertheless, where loss of time due to operating difficulties is important, or where skilled technical assistance is not available, the sealed-tube X-ray diffraction unit generally is preferred.

In addition to the foregoing filament, or hot-cathode, types, so-called gas tubes are sometimes employed, although less frequently now than formerly. In these the supply of electrons is obtained from the impacts of positive gaseous ions on the cathode and a small pressure (0.004 to 0.001 mm. of mercury, in the case of air) is maintained in the tube during operation. Gas tubes are relatively inexpensive and can be made in any competent machine shop. They are readily demountable for cleaning and interchange of targets, but they usually require considerable technical skill for successful operation.

Depending on the wave-length of the X-radiation desired, and on the physical properties of the target metal, potentials of the order of 35 to 60 kV usually are employed in X-ray diffraction investigations.

X-radiation belongs to the same class of phenomena as the gamma rays from radio-active sources, ultra-violet rays, visible light, infra-red rays, radio and electric waves, all of which, on the basis of classical electrodynamics, are electromagnetic waves. The wave-lengths comprising the X-ray band of the spectrum lie between those of the gamma rays and those of the ultra-violet. For purposes of comparison, the characteristic (Kα) wave-lengths of certain metals frequently used as target materials in X-ray tubes are as follows: molybdenum (Mo), 0.7107 A; copper (Cu), 1.5418 A; cobalt (Co), 1.7902 A; iron (Fe), 1.9373 A; chromium (Cr), 2.2909 A, where 1 A$=10^{-8}$cm., while the wave-length of the yellow D-line of sodium, in the visible region, is about 5890 A. Although all electromagnetic waves have a corpuscular character in many of their manifestations, attention can be confined almost exclusively to their wave nature for purposes of the present discussion.

Like visible light, X-rays travel in straight lines and are differentially absorbed by matter but, due to their much shorter wave-lengths, they can penetrate many substances opaque to visible light. To these properties are due the wide-spread applications of X-radiography for the study of otherwise hidden objects and conditions by means of shadow photographs (radiographs) and fluoroscopy.

Since X-rays are not visible they must be observed indirectly by their action on photographic emulsions or on fluorescent materials. X-radiation has marked biological effects so that suitable safety precautions for operating personnel must be observed. Finally, X-rays undergo reflection, refraction and diffraction as does visible light, but modified in scale due to their shorter wave-lengths.

The diffraction of X-rays by crystalline powders

For centuries it has been realized that the geometrical regularity of the forms exhibited by single crystals must be due to correspondingly regular arrangements of their constituent atoms or groups of atoms. The discovery of X-radiation by W. C. Röntgen in 1895, and the pioneering work of M. von Laue in 1912, followed and expanded immediately by W. H. Bragg and W. L. Bragg, on the interaction of X-rays with crystalline matter not only verified this belief but has led to the elucidation of the detailed structure of a vast number of crystals, many of them of extreme complexity. The application of X-ray diffraction techniques to the study of crystalline powders, with which this paper is concerned, was devised in 1916 by A. W. Hull and by P. Debye and P. Scherrer, and the X-ray diffraction powder method frequently is referred to as the Hull, the Debye-Scherrer, or the Hull-Debye-Scherrer method.

A crystal is built up of a periodic three-dimensional arrangement of atoms, ions, or groups of atoms. These repeat units may be visualized as situated at the points

of a three-dimensional net, called a space lattice, such as that shown in figure 1. Thus, if an observer were stationed at any point (say, G) in the lattice and moved along each of any three straight lines (say, GH, GE, GC) he would encounter a series of points along each line, separated by exactly the same distance and equivalent to one another in all respects. Consequently, an observer at point G of the lattice represented in figure 1 could not distinguish his point of observation from point H, or E, or C, or any other point of the lattice; his surroundings would be identical in all cases. The three basic lines GH, GE, GC, in direction and in length, therefore, define the particular lattice of figure 1. These three lines also define the edges of a box, called a unit cell, ABCDEFGH, and the complete space lattice may be constructed by the regular stacking in three dimensions of an infinite number of these unit cells. The lengths (a, b, c) of the edges of the unit cells may be equal or unequal as may the angles (α, β, γ) that they make with one another. An examination of figure 1 will show that the points of the lattice can be joined by other sets of lines defining unit cells of different shapes from the particular one outlined. There are, however, certain rules on which the choice of lines defining the edge lengths and angles of the unit cell in a given structure is based and all crystal structures can be referred to fourteen basic lattice types.

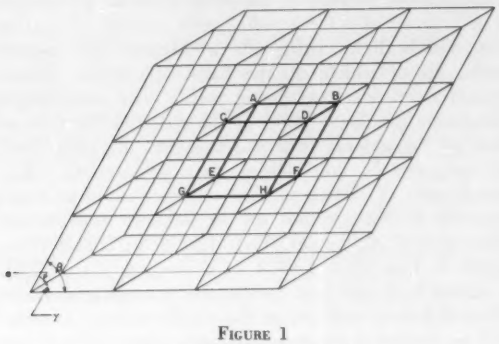


FIGURE 1
Space lattice and unit cell

For the present purpose, however, it is sufficient to recognize that, regardless of how the unit cell and hence the lattice is selected, all points of the lattice lie on sets of parallel planes. The planes of each set are separated by the same perpendicular distance apart, or interplanar spacing, d, which is characteristic of that set. Thus, in figure 1, ABCD and EFGH lie on two adjacent planes of a set of equidistant parallel planes, ABEF and CDGH lie on another set with a different spacing, and so on. The plane faces of well-developed crystals are simply an outward manifestation of this fact; they are parallel to sets of planes within the crystal structure and these planes usually are those having a relatively large number of atoms per unit area.

For each crystalline material either the detailed spatial arrangement of the atoms, or their distances apart, or, in most cases, both factors are virtually unique. Thus, each crystalline substance may be distinguished by its specific collection of sets of parallel planes and, consequently, by a characteristic series of d values. Although coincidence of individual spacings may occur, only very rarely are all the spacings of one substance so nearly equal to all those of another that there is any ambiguity in their differentiation. Furthermore, the chance of such complete coincidence occurring in the case of organic compounds, such as the narcotics, which have relatively large unit cells and relatively low symmetry, is extremely small. As shown later, there is a lower limit to the values of d that can be measured experimentally through the use of X-radiation of a given wave-length. The larger the maximum value of d, therefore, the greater will be the number of interplanar spacings potentially measurable. Also, in crystals of high symmetry, several sets of planes have the same spacing (e.g., those on which lie the pairs of parallel sides of the unit cell in the cubic system) while in those of lower symmetry e.g., monoclinic) there are fewer sets of planes the spacings of which are identical, thus increasing the number of different d values that may be determined. As a general rule, therefore, if a reasonable number (say, 10 or more) spacings (d) of the sets of planes on which the constituent atoms of a given crystalline substance are situated can be measured (with an accuracy of 1 or 2 per cent or better) the characterization of that substance for identification purposes will have been achieved.

When a narrow, parallel beam of X-rays is directed through a crystal, the electrons in the atoms of which it is composed are set into forced oscillation, and this disturbance results in each atom acting as a source from which radiates a secondary set of spherical waves of the same wave-length as the incident rays. Due to the regularity in the spatial arrangement of the atoms these scattered wavelets enhance each other in certain directions, where they are in phase, and tend to annul one another in directions in which they are not in phase. The crystal, therefore, acts as a three-dimensional diffraction grating towards the incident X-radiation and a number of diffracted rays emerge from it at certain definite angles and with certain definite intensities.

The mathematical treatment of the diffraction of X-rays by the crystal lattice is simplified by considering the effect as due to reflection of the incident X-ray beam by the sets of parallel planes of characteristic spacings (d) on which the atoms of the crystal are located. This reflection differs from the optical case of light reflected by a plane mirror because it takes place from a set of many equidistant parallel planes simultaneously and not solely at the surface. For this reason, X-ray reflection from a crystal occurs only for certain angles of incidence; reflection of light from a plane mirror takes place at any angle of incidence. The Bragg equation, $n\lambda = 2d \sin \Theta$ (for which a simple derivation is illustrated in figure 2) expresses the relationship between the wavelength (λ), the spacing (d), and the angle of incidence (Θ), that must be satisfied in order that X-ray reflection shall occur. The rays reflected from successive planes

must be a whole number ($n = 1, 2, 3, \ldots$) of wave-lengths apart in order that they shall be in phase and thus enhance each other (as shown in figure 2 for three

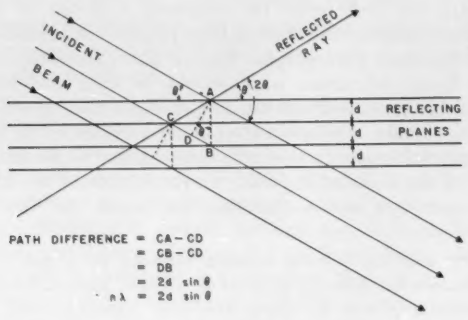


FIGURE 2
Derivation of the Bragg equation

successive planes of spacing (d)). For a given set of planes a series of reflections (first, second, third, etc., order) are obtained at different angles of reflection (Θ) for a given wave-length (λ), depending on n (i.e., depending on whether the rays from successive planes are 1, 2, 3, . . . wave-lengths apart). It is customary, however, to consider all reflections as first order and to write the Bragg equation in the form: $\lambda = 2(d/n) \sin \Theta$, or simply, $\lambda = 2d \sin \Theta$, thus treating the n^{th} order reflection from a set of planes of spacing d as if it were the first order reflection from a set of planes of spacing d/n. Taking the spacings in this sense, the Bragg equation contains three variables (λ, d, and Θ) so that if any two (e.g., λ and Θ) can be fixed, or measured, experimentally the third (e.g., d) can be determined.

In the Laue method a beam of X-rays comprising a continuous band of wave-lengths (the so-called "white" radiation) is directed through a stationary crystal. In this case, Θ for each set of planes in the crystal is fixed but each set reflects rays of the particular λ required to satisfy the Bragg equation for its particular value of d. More commonly, however, a beam of essentially monochromatic X-rays (fixed λ) is employed and the orientation of the crystal is varied during exposure so that different sets of planes are brought successively into reflecting position (i.e., Θ is varied continuously and the values at which reflections occur are observed).

A crystalline powder consists of a very large number of very small single crystals. If the powder is very finely divided, a small, randomly selected, sample will generally contain crystals in all possible relative orientations. Thus, for the reflection of a given wave-length λ by a particular set of planes of spacing d, at least a few individual crystals will be in such position that this set of planes makes the appropriate angle Θ with the direction of the incident beam. Therefore, each set of planes characterizing the structure of the particular substance will, in different crystals of the powder, be in correct reflecting position, and all possible reflections will occur simultaneously. Furthermore, assuming completely random orientation, individual reflections from a given set of planes, but from different individual crystals, will be distributed over the surface of a cone having the incident X-ray beam as axis, and a semivertical angle 2Θ, governed by the interplanar spacing d and the wave-length λ. In figure 2 it will be observed that the reflected ray makes an angle 2Θ with the incident beam. If such a set of planes be rotated about the incident beam as axis, the reflected ray will generate a cone of semivertical angle 2Θ, as illustrated in figure 3 for a ray in the transmission region ($2\Theta_1 \leqq 90°$) and for one in the back reflection region ($2\Theta_2 \geqq 90°$). The same effect is achieved from a large number of stationary crystals in completely random orientation; at least some will be distributed in all angular positions around the incident beam while a given set of planes, in separate crystals, maintains the required angle of incidence Θ for reflection to occur. If relatively few crystals are in correct orientation, the reflections will emerge as discrete rays along the surface of the cone; if a large number of crystals are in reflecting position, the individual rays will merge to cover the surface of the cone completely and uniformly.

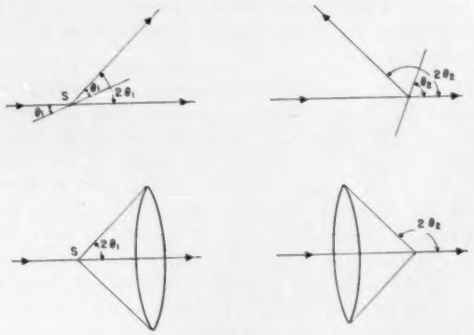


FIGURE 3
X-ray diffraction comes from a crystalline powder

From the randomly orientated crystals of a powder sample, therefore, a family of coaxial cones of reflected rays is obtained. The cone angles 2Θ depend on the spacings d characteristic of the crystal structure and on the wave-length λ of the incident beam. Now 2Θ may have any value from 0° to 180° so that observable values of Θ extend from 0° to 90° and sin Θ values cover the range from 0 to 1. Furthermore, since $d = \lambda/2 \sin \Theta$, the smallest measurable value of d is equal to $\lambda/2$. Finally, for a fixed value of d, sin Θ is directly proportional to λ so that better dispersion of the reflection cones (i.e., 2Θ values) is obtained with longer wave-lengths.

In addition to these purely geometrical features that enable a given crystalline substance to be characterized in terms of a series of interplanar spacings, each reflection has a definite intensity, determined by the particular

atoms concerned, the geometrical spatial arrangement of the atoms, the wave-length of the radiation, and certain other factors. Although reflection intensities are of the greatest importance in the elucidation of crystal structures, they serve largely for verification purposes in powder identification and as a convenient basis for the classification of d values. Thus if two substances have similar structures with unit cells of almost the same size and shape, there may be some difficulty in differentiating one from the other solely on the basis of their very similar interplanar spacings d. Since their constituent atoms are not the same, however, the relative intensities of reflections from planes of similar spacings in the two substances generally will be different. A few cases have been encountered (4) where two very different substances give virtually the same powder pattern both with respect to interplanar spacings and relative intensities, but such coincidences are rare.

The measurement of interplanar spacings (d) and the estimation of relative intensities (I/I_1)

Two general methods are employed for recording the X-ray diffraction pattern from a crystalline powder. The Geiger spectrometer utilizes the property of X-radiation of ionizing a gas through which it passes, and the powder camera makes use of the effect of X-radiation on a photographic emulsion.

The Geiger spectrometer is rapidly becoming very popular for X-ray diffraction studies. With this instrument the 2Θ values for successive reflections from a powder sample are measured in terms of the angles through which a Geiger-Müller counter must be turned about the sample as centre to receive the reflected rays. The counter consists essentially of a metal cylinder filled with a suitable gas. A potential difference is maintained between the walls and a metal wire stretched along the axis of the cylinder. When X-radiation enters the counter the gas is ionized and a discharge takes place between the wire and the walls. In this application the X-rays behave as particles and a discharge occurs for each X-photon that enters the counter. Thus the number of discharges per unit time is proportional to the rate at which X-photons are received, and, therefore, to the intensity of the X-radiation. By means of an appropriate electronic circuit the number of X-photons entering the Geiger tube is counted and the counting rates are translated into a line on a moving chart. From the distances apart of peaks on the chart, corresponding to reflections from the sample, the $2\ \Theta$ values are obtained, and after suitable calibration, intensities are determined from the heights of the peaks.

When relatively large samples are available the Geiger spectrometer is both accurate and rapid, although some skill in specimen preparation is necessary for best results. Special sample holders have been devised for specimens of a few milligrams weight. If quantities of only a milligram or less are available, as is frequently the case in a narcotics investigation, the Geiger spectrometer is less reliable and more time-consuming than the photographic method.

For very small samples, therefore, the powder camera is still the best means for obtaining a record of the diffraction pattern of a crystalline powder for identification purposes. Photographic films or plates recommended for X-ray diffraction work should be used and they should be processed with the developer and fixer specified for the emulsion selected. Over a considerable range the photographic density is directly proportional to the intensity of the X-radiation falling on the surface of the film per unit area and to the time for which the film is exposed.

The simplest powder camera consists of a pin-hole collimator for defining a pencil of virtually parallel monochromatic X-rays of about 0.5 mm. diameter, and a cassette to take a flat photographic plate with its surface normal to the X-ray beam. The diffraction cones from a powder sample intersect the flat plate in concentric circles from the radii of which, and the distance from the sample to the plate, the corresponding values of $2\ \Theta$ are obtained as illustrated in figure 4. Interplanar spacings (d) may then be calculated with the aid of the Bragg equation and a knowledge of the wave-length (λ) of the X-radiation employed. The flat plate camera, however, is seldom used. In the first place only a limited number of diffraction cones in the transmission (small $2\ \Theta$) region can be recorded. Secondly, the length of path through which a reflected ray must travel to reach the plate

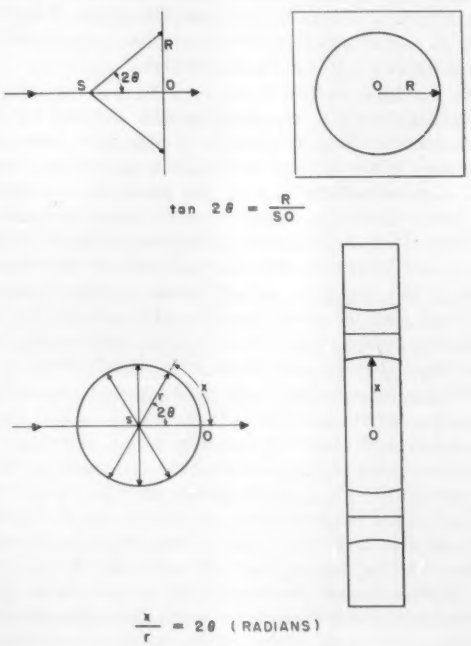


FIGURE 4
Measurement of flat plate and cylindrical film

increases as 2 Θ increases, thus reducing the intensity by increasing air scatter and aggravating the normally rapid decline in intensity characteristic of organic compounds. Finally, as 2 Θ increases, the reflected rays traverse the emulsion with increasing obliquity thus broadening the lines of the diffraction pattern and impairing their resolution.

Generally, therefore, the camera is in the form of a cylinder with the sample, preferably also of cylindrical shape, at the midpoint of the axis which is there intersected at a right angle by the collimated X-ray beam. All reflected rays lying on a circle, normal to the axis of the cylinder and passing through the incident X-ray beam, travel outwards from the specimen along radii of the camera. All such rays, therefore, traverse the same distance and pass through the cylindrical strip of photographic film, lining the inside surface of the camera, normal to its surface. With this type of camera, all possible reflections from $\Theta = 90°$ to $\Theta = 0°$ can be recorded, except for a small region at $2\Theta = 180°$ masked by the collimator, and a similar one at $2\Theta = 0°$ covered by some device for the removal of the undiffracted portion of the direct beam.

The choice of the radius of a cylindrical camera is largely one of compromise between exposure time and resolution. For a given X-ray wave-length, the larger the camera radius the greater will be the separation of the cones of reflection when they intersect the film. On the other hand, the length of path between specimen and film increases, resulting in increased scattering of the reflected rays by air molecules. This reduces the intensity so that a longer exposure is required to obtain a pattern of reasonable photographic density, and the scattered radiation appears on the film as an increase in the general background fogging.

In Great Britain a camera diameter of 90 mm. for general use, and 190 mm. for precision measurements, has been recommended by the X-Ray Analysis Group of the British Institute of Physics. A popular diameter in France is 76.4 mm. in which a length of 1 mm. on the film represents a 2 Θ angle of 1.5°. Although cameras of several diameters are common in North America, there is a trend towards the standardization of diameters of 57.3 mm. and 114.6 mm., the first for patterns in which resolution is not critical or when relatively short exposure times are desirable, the second for more complex patterns. The obvious advantage of these diameters is that 1 mm. on the film represents a 2Θ value of 2° in the first case and 1° in the second, thus reducing the conversion of film measurements into reflection angles (Θ) to simple mental arithmetic.

In the processed photograph the intersections of the reflection cones with the circular strip of film appear as curves, concave towards the point corresponding to $2\Theta = 0$ if $2\Theta < 90°$, a straight line at $2\Theta = 90°$, and concave towards the point corresponding to $2\Theta = 180°$ if $2\Theta > 90°$, as shown in figure 4, where the determination of 2Θ from linear measurements of the flattened-out film and the known camera radius is illustrated. In actual practice, measurements ($2x$) usually are made from arc to arc across the centre (0, figure 4). For cameras of 57.3 mm. and 114.6 mm., values of $2x$ are merely divided by 8 and 4, respectively, to obtain Θ directly in degrees. In other cameras a less simple conversion factor must be used, or a chart may be prepared for conversion of film measurements (in mm.) to Θ (in degrees). Interplanar spacings (d) can be calculated from the Bragg equation, or may be obtained from tables of d vs. Θ [16], or from transparent scales of d values prepared for the particular camera and wave-length used and superposed directly on the film. This last method is the most rapid since no film measurements or determinations of Θ are involved.

Several methods of mounting the film in a cylindrical camera are shown diagramatically in figure 5. In what may be termed the normal method, the ends of the strip of film are at the collimator. The undiffracted portion of the beam is prevented from fogging the film directly in front of the collimator by a beam trap of lead that absorbs the radiation, or by providing an exit tube that passes through a hole punched in the film. With the van Arkel mounting the film is reversed; the collimator goes through a hole in the film the ends of which are at the exit tube. More convenient and precise determinations of interplanar spacings in the back reflection region are possible with this type of film mounting but it is unsuitable for organic substances for which lines of large 2Θ angles usually are not observed.

The most convenient mounting is that due to Straumanis in which the ends of the film meet at a line corresponding to $2\Theta = 90°$ and holes are punched in the film for insertion of both the collimator and the exit port. Since the distance between the holes in the unprocessed film substends an angle at 180°, its measured length after the film is developed may be used to determine the extent of any shrinkage that has occurred during processing of the film. If significant shrinkage is found, a correction is applied to the measurements of the diffraction arcs. If arcs are present in both the transmission and back reflection regions they are used to determine the effective centre of each hole. If there are none in the back reflection region, which usually is the case with narcotics, film shrinkage can be estimated by measuring across the diameter of each hole to determine the centre-to-centre distance between them and comparing this value with that obtained from similar measurements on a strip of film that has been cut and punched but has not been processed. Alternatively, the Wilson modification of the Straumanis film mounting may be employed in which the ends of the film meet at a line corresponding to a 2Θ value of approximately 40°. This ensures that measurable lines of relatively low 2Θ will bracket each hole in the film as shown in figure 5. Either the Straumanis or the Wilson method of film mounting is highly satisfactory for powder photographs of organic compounds.

For most practical purposes it is sufficient to grade the intensities of the reflections visually, in terms of the

relative density of the lines of the powder pattern, as strong (s.), medium (m.), weak (w.), interpolating with v. (very), s., s.m., m.w., v.w., etc. It has, however, become customary to place these estimates on a numerical scale relative to 10, or 100, for the strongest line, thus (1), v.v.s, 100; v.s., 90; s., 80; m., 70, 60, 50; w., 40, 30; faint, 20; very faint, 10. Such relative intensities are tabulated under the symbol, I/I_1 (i.e., the ratio of the intensity of each line to that of the most intense which is referred to as the strongest, or first, line).

Visual estimations theoretically can be improved by comparison of each line of the powder photograph with a calibrated intensity scale (7). Such a scale can be prepared by exposing a strip of film for predetermined times for an X-ray beam of constant intensity defined by slits to produce lines of approximately the same width as those of the powder pattern.

The use of a microphotometer, such as those employed for spectroscopic plates, is not necessary in most powder identification work. It is more time-consuming than visual estimations and may actually be misleading due to the relatively high background intensity of many X-ray diffraction powder films.

Identification from X-ray diffraction powder data

The identification of a substance from its X-ray diffraction powder data requires the comparison of its pattern with those of authenticated standards until a perfect match is found. Such a search may be carried out with the films themselves, in which case the standard powder photographs with which they are compared should be those taken in a camera of the same radius and with the same X-ray wave-length. Alternatively, tabulated data for d (independent of camera radius and X-ray wave-length) and I/I_1 may be employed.

Several years ago, Hanawalt, Rinn, and Frevel (7) proposed what has now become a standard system of identification based on values of d and I/I_1. In the A.S.T.M. index of X-ray powder data (1), X-ray powder patterns are classified according to the spacings (d) of the three lines of strongest relative intensity (I/I_1). Separate cards for each pattern are filed in groups of limited ranges of d for their strongest line ($I/I_1 = 100$). Within these Hanawalt groups they are placed in numerical order of d for the second strongest line and, where these happen to be equal, the order of the third strongest line is followed. The cards also carry the d and I/I_1 values for the complete pattern and other pertinent data about the substance. A search of the file involves selecting the Hanawalt group within which the d of the strongest line of the unknown pattern occurs, going through these cards for the d of the second strongest line and checking by means of the d of the third strongest line. If a card for a substance with the same (or nearly the same) d values as those of the unknown for the first, second, and third lines is found, the complete set of d and I/I_1 values on the card is compared with that of the unknown. In such a search and comparison some allowance, of course, must be made for permissible small variations in d due to unavoidable differences in film measurements, and in I/I_1 due to the fact that the intensity of diffraction from the same set of planes of the same substance is not independent of the wave-length but is affected to some extent by both λ and $\sin \Theta$. Furthermore, since personal differences in appraisal of I/I_1 for lines that are of almost equal photographic density may place the three strongest lines in different order, it is convenient to use a three-card set in which triplicate cards are filed in the order 1, 2, 3; 2, 1, 3; 3, 1, 2. Complete coverage by including cards for the remaining combinations 1, 3, 2; 2, 3, 1; 3, 2, 1 would make the system too unwieldy in view of the fact that the file already contains cards for about 4,800 patterns (14,400 cards in a three-card set). The data cards are available in three forms; plain for manual sorting, punched for mechanical (Keysort, Copeland-Chatterton) sorting (12), and punched for machine (International Business Machines (I.B.M.), Hollerith) sorting (11).

Due to the fact that the A.S.T.M. index includes data from a large number of laboratories obtained under various conditions and with different degrees of care and accuracy, it is not surprising that it should contain some erroneous entries. For this reason, and for the satisfaction of complete certainty in an identification, it is desirable to build up a standard file of diffraction patterns to be used in conjunction with it. Furthermore, in many cases there is sufficient preliminary evidence or suspicion of the identity of an unknown to warrant rapid direct comparison of the powder photograph with those of authenticated standards selected from such a file. Even when an identification is made in the normal way with the index it is a matter of convincing satisfaction to be in a position to match the photograph obtained from the unknown with one from a standard file.

For a laboratory dealing largely with organic substances it must be admitted that the present A.S.T.M. index contains a preponderance of data on inorganic materials, although the situation is improving rapidly as more X-ray diffraction powder patterns for organic compounds become available. Although it is highly desirable that any laboratory devoted extensively to identification by the X-ray diffraction powder method should have at least a one-card set of the A.S.T.M. index, a specialized narcotics laboratory at the present time probably could set up its own filing system of data cards and standard X-ray diffraction patterns of the substances most likely to be encountered that would be less costly and almost as useful.

Preparation and size of specimens, choice of radiation, and the time factor

An ideal powder pattern consists of lines that are narrow, sharply defined, and well resolved. Each line should be continuous and of uniform intensity. Background fogging should be negligible. Photographs satisfying all these criteria require special precautions that

increase the time required to prepare the sample and record the diffraction pattern. In cases where identification is the primary object, the time factor usually is important and some compromise with ideal conditions must be tolerated.

Occasionally the nature of the specimen itself, such as distortion of the crystal lattice, excessive thermal vibration of the constituent atoms, or excessively small particle size, may cause diffuse and broadened lines. Improvement can sometimes be effected by annealing the specimen, by reducing the temperature during exposure in the camera, or by recrystallization, but even these expedients are not always practical or successful.

In general, however, satisfactory photographs can be obtained in a cylindrical camera with a reasonably fine (*circa* 0.5 mm.) slit or pin-hole collimating system and a specimen of approximately cylindrical shape of diameter slightly less than that of the collimated X-ray beam. The specimen should be mounted with its axis coinciding with that of the camera. It should be rotated about this axis continuously during exposure to ensure that complete randomness of orientation of the crystals is achieved.

The best powder photographs are obtained from specimens in which the particle size is of the order 10^{-3} to 10^{-6} cm. Above this range the lines become spotty in appearance even with rotation of the sample because there are not sufficient crystals in a small volume to ensure completely random orientation. With particles of sizes less than a few hundred angstrom units not enough parallel planes remain in a given set, of spacing d, for the rigid validity of Bragg's equation and a sharp diffraction angle Θ; diffraction takes place over a wider angular range and the lines on the photograph become broader and more diffuse.

Many samples of narcotics consist of crystals that are larger than the optimum size and these require grinding before the specimen is prepared for a powder photograph. Like many organic crystals they tend to be soft and if ground in the usual way with an agate or mullite pestle and mortar they may smear over the surface. Very small samples can be ground with less difficulty and waste by using a well-type microscope slide as mortar and a short length of drawn-down glass rod or tubing, rounded at the end, as pestle and observing the operation under a steroscopic microscope, or a fine needle may be used to break down individual crystals to a suitable size. Very fine needles may be prepared by fixing a length of tungsten wire (1 mm. diameter) in a brass handle and dripping the end of the wire into molten sodium nitrite. The taper can be regulated by the rate at which the wire is dipped into and withdrawn from the melt and it is essential to have the sodium nitrite very hot.

The speciments for the camera may be made by coating a hair or a very fine glass fibre with the powder mixed with an adhesive, or the glass fibre may be smeared very thinly with vaseline and the powder taken up on it. A support can be eliminated if the powder, mixed with a binder, is extruded by means of a piston through a small orifice in a cylinder, or the mixture can be rolled out between two microscope slides or with the fingers. Very small samples (of the order of 0.01 mg.) can be picked up in a drop of household cement on the end of a glass fibre. A form of mount that normally requires no binder or adhesive is wedge-shaped, with a small section of the edge of the wedge cut out and packed with the powder; the X-ray beam is directed through the sharp edge of the specimen. Thin-walled pyrex or Lindemann glass capillaries, or collodion tubes, may be used and are especially useful if the sample is deliquescent or efflorescent.

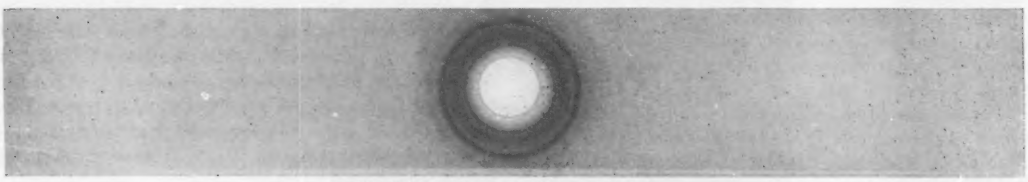
Care must be exercised in the selection of adhesives or binders because they may add diffraction lines of their own to the pattern. This is particularly true of vaseline if more than a trace is used. Even if truly amorphous, adhesives and binders should be employed sparingly because their presence increases the general background density of the photograph due to scattering of the radiation, and they may also produce broad diffuse haloes in the small 2Θ region. In any case it is advisable to test a selected material by an X-ray diffraction photograph before adopting it.

The choice of a suitable X-ray wave-length depends on a number of factors. The unit cells of organic crystals usually are large so that they commonly have relatively high maximum values of d. Thus the powder pattern extends to relatively small values of 2Θ and, with very short wave-lengths, the innermost (closest to $2\Theta = 0°$) lines may occur within the area of the film occupied by the beam trap, or exit port, of the camera, in which case they will not be recorded on the film. Furthermore, organic crystals frequently belong to the crystal classes of lower symmetry so that their patterns are characterized by a large number of lines, many of which correspond to very similar d values. Finally, the relative intensities of reflections from organic crystals tend to decrease very rapidly with increasing 2Θ angles so that the observable lines of the powder pattern generally occur only in the transmission (small 2Θ) region of the film. For these reasons it is desirable to increase the 2Θ angles as much as possible. For a given set of d values this can be done by using X-radiation of maximum wave-length since, from the Bragg equation, $\sin \Theta$ is directly proportional to λ. Unfortunately, the longer wave-lengths are highly absorbed and scattered by the air in the camera. This not only increases the exposure time for a satisfactory photograph but also increases the background density of the developed film, thus rendering it more difficult to recognize and measure lines due to very weak reflections. The effect can be minimized by partial evacuation of the camera, or by filling it with hydrogen, but such procedures normally are not desirable in routine identification work. Another method of increasing the dispersion of the lines on the powder photograph is to increase the diameter of the cylindrical camera. This is of limited practical effectiveness, however, due to increased exposure times and background fogging resulting from the increased absorption and scatter of the reflected rays before they reach the film.

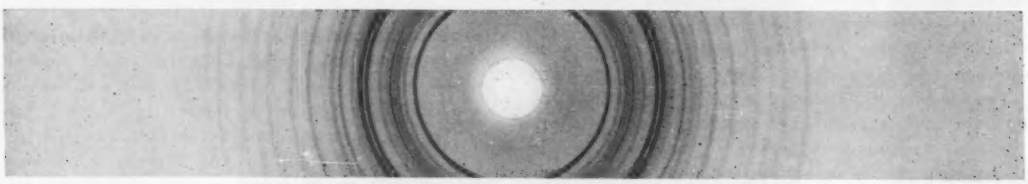
While many data in the A.S.T.M. index have been obtained with Mo radiation (λ (Kα) = 0.7107 A), the one most commonly employed for inorganic compounds is that of Cu (λ (Kα) = 1.5418 A) except in the case of substances containing a high proportion of cobalt, iron, manganese or chromium. These elements absorb much of the energy of copper radiation and radiate their own characteristic wave-lengths. This fluorescent radiation appears on the powder film as a marked increase in the background fogging. Hence cobalt (λ (Kα) = 1.7902 A), iron (λ (Kα) = 1.9373 A), and chromium (λ (Kα) = 2.2909 A) radiations, respectively, frequently are used for samples containing these elements. Unfortunately, X-ray tubes with targets of these metals usually cannot be operated at as high potentials and tube currents as those with anticathodes of molybdenum or copper. Chromium radiation frequently is employed for powder photographs of organic substances (13) because of the much improved dispersion of the lines obtained with its use. Due to air absorption and scatter, however,

FIGURE 5

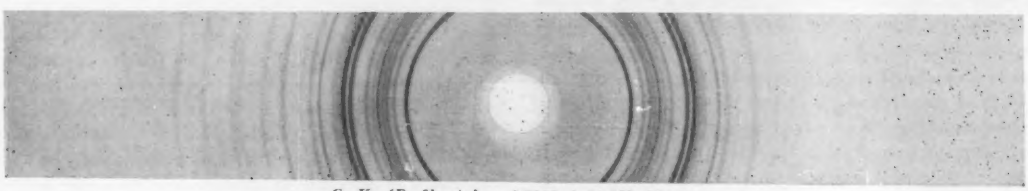
EFFECT OF λ ON X-RAY DIFFRACTION POWDER PATTERNS
(Papaverine; 114.6 mm. dia. camera; Straumanis film mounting; transmission end of films; 8-hour exposures)



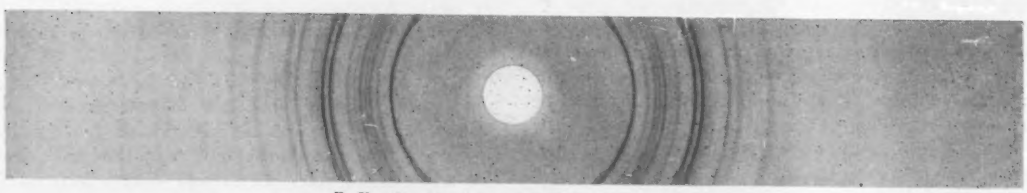
Mo Kα (Zn filter), λ = 0.7107 A, 50 kV., 20 ma.



Cu Kα (Ni filter), λ = 1.5418 A, 30 kV., 20 ma.



Co Kα (Fe filter), λ = 1.7902 A, 30 kV., 11 ma.



Fe Kα (Mn filter), λ = 1.9373 A, 30 kV., 15 ma.

Cr Kα (V filter), λ = 2.2909 A, 30 kV., 22 ma.

exposure times are increased appreciably. Thus, whereas 99 per cent of Mo Kα radiation is transmitted by 10 cm. of air, only 68 per cent of Cr Kα radiation penetrates the same distance.

To ensure a clean film background, free from fog, strictly monochromatic radiation should be used but the special technique required rarely is justifiable in simple identification problems. X-ray tubes for powder investigations usually are operated at voltages that excite the characteristic K lines of the target metal with maximum intensity relative to that of the unwanted continuous radiation. The K series consists essentially of three lines, a pair ($K\alpha_2$, $K\alpha_1$) having wave-lengths separated by only about 0.004 A, and one (K β) of appreciably shorter wave-length; their relative intensities are $K\alpha_2$: $K\alpha_1$: $K\beta$ = 50 : 100 : 22. In practice it is very difficult to separate $K\alpha_2$ and $K\alpha_1$ although in a good powder photograph they are resolved for large 2 Θ angles as represented by the double lines in figure 5. The K β line can be removed effectively from the incident beam by interposing a suitable filter between the X-ray tube and the camera. Thus zirconium, nickel, iron, manganese, and vanadium are employed to reduce the intensity of the Kβ line of molybdenum, copper, cobalt, iron and chromium, respectively. The mass per square centimetre and the thickness of the filter are chosen so as to reduce the Kβ radiation to about 1/600 of that of the Kα; this ensures that diffraction lines due to the former will not be recorded on the photographic film in the time required to obtain a good photograph of those due to the Kα radiation.

The influence of X-ray wave-length on the appearance of the powder pattern is illustrated in figure 5 by X-ray diffraction powder photographs of papaverine taken with molybdenum, copper, cobalt, iron, and chromium radiation (Kα), respectively. The same (114.6 mm. diameter) camera, the same (8 hours) exposure time and (except for the first) the same sample were used in each case. Straumanis film mounting (see figure 6) was employed but only the transmission (small 2Θ) end of the film strips is reproduced. The unsuitability of molybdenum radiation for powder photographs of complex organic substances is so obvious from figure 5 that no comment is necessary. The photographic density of the lines in the pattern obtained with copper radiation indicates that a much shorter exposure time would have been sufficient to produce a record suitable for identification; resolution is adequate in the case of the papaverine pattern but it is apparent that serious overlapping of lines would occur in those with smaller line separations. The dispersion of the lines improves progressively with the use of cobalt, iron, and chromium radiation but (for a fixed exposure time) the photographic density decreases in the same order. In this laboratory, cobalt (Kα) radiation is favoured for powder photographs of most organic substances; dispersion of the lines is better than that obtained with copper radiation, exposure times for acceptable photographs are lower than those required with iron or with chromium, and resolution usually is sufficient for identification purposes.

A relatively large sample (of the order of 0.15 mg.) was employed for the photographs reproduced in figure 5. It was mounted by taking it up in a drop of household cement on the end of a glass fibre. With cobalt radiation a pattern of sufficient density for identification can be obtained in about 5 hours from such a sample of most narcotics. An effective reduction in this exposure time by a factor of about 4 can be achieved by intensification of the X-ray film after normal processing. The necessary solutions (3) are easy to prepare and the procedure adds only 30 minutes to the normal time for development and fixation.

A somewhat larger sample is required if it is necessary to place it in a thin-walled capillary tube. This method of specimen mounting, however, ensures a cylindrical shape, and usually improves the resolution of the lines on the powder photographs. Owing to absorption by the tube, exposure times tend to be increased to about 7 or 8 hours for satisfactory results. As a practical example, the

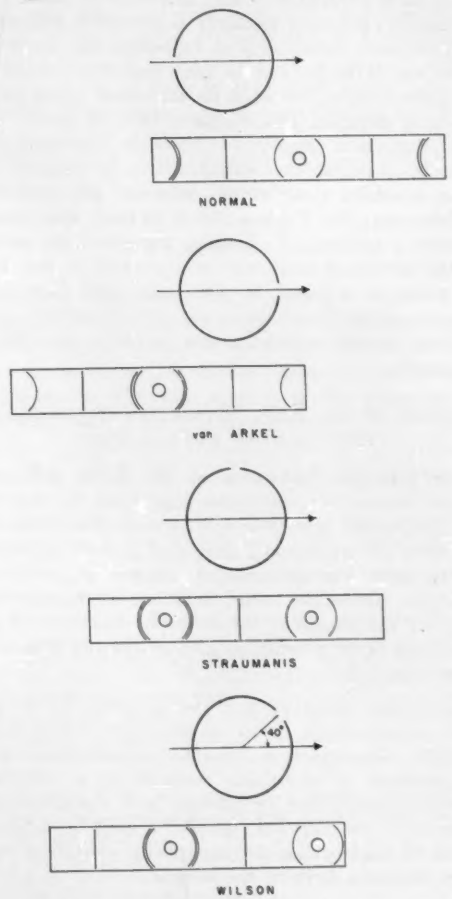


FIGURE 6
Types of film mounting

powder patterns of 40 different narcotics samples have recently been obtained and compared with standard patterns in this laboratory in a period of 10 days. Two powder cameras were used with cobalt radiation, and the samples were mounted in capillary tubes. Exposures times were about 7 hours during the day and 15 hours overnight. The shorter exposures were satisfactory; the longer ones gave more complete patterns but were not strictly necessary. The films were not intensified.

Samples are small as 0.01 mg. can be picked up in a drop of household cement on a glass fibre and their powder patterns may be obtained without recourse to special microtechniques. Exposure times, of course, are longer than those required for average specimens of the order of 0.1 mg.

Although the time required to identify the unknown sample depends on a number of factors, including the size of specimen available, it is possible in most cases to complete an identification during the afternoon if the unknown is received by 9 a.m. Alternatively, since X-ray diffraction equipment normally is provided with timers and automatic cutout devices, exposures may be started at the end of the day and the films may be processed and the patterns identified when the laboratory opens on the following morning. This compares very favourably with other methods of complete identification. The assumption is made, of course, that standard data, or standard patterns, matching those of the unknown are present in the laboratory file. If this proves to be false, identification becomes a problem of obtaining patterns from authenticated substances until one corresponding to that from the unknown is found. In such cases data from other sources and other techniques can be very helpful in indicating possible substances that should be included in the search.

Appraisal of the X-ray diffraction powder method for narcotics identification

The principal limitations of the X-ray diffraction powder method of identification arise from the facts that (*a*) it is readily applicable only to crystalline materials; (*b*) there are occasional instances of possible ambiguity due to very close similarity of patterns on account of structural similarities, solid solution, or isomorphism (4); (*c*) the sensitivity toward small quantities of one constituent in the presence of a large quantity of another is not very high.

Amorphous materials give rise to broad haloes and much general scatter so that identification usually is not practical, although it is possible in favourable cases. The presence of amorphous material in an otherwise crystalline sample may be inferred from the general appearance of the film but, usually, a definite statement cannot be made unless the amorphous constituent comprises the main bulk of the sample.

Almost identical patterns may be obtained from crystals which have very similar structures and in which the atoms have similar scattering effects on X-rays. This is particularly apt to be the case if the two structures are actually isomorphous. Such ambiguities, however, may be expected to be confined to the simpler inorganic structures of high symmetry (e.g., cubic, tetragonal), although some difficulty may be encountered in differentiating among isomorphous hydrohalide salts of organic bases having large molecules.

Solid solutions involve the replacement of one atom by another of comparable size in the crystal lattice. The result is a small change in the interplanar spacings (d) that frequently can be detected only by the use of high precision techniques. This difficulty, however, usually is of major importance only in the study of metals, alloys, and minerals.

All crystalline constituents of a mixture contribute their patterns to the powder photograph so that the analysis of such a system becomes a problem of separating and identifying the individual sets of lines characteristic of each. With complex powder patterns, such as those of the narcotics, there is a high probability of coincidence of some lines, and resolution is likely to be impaired due to the lines of one constituent appearing among the already crowded lines of another. In particular cases it may be necessary to sacrifice exposure time in favour of greater dispersion of the pattern by the use of chromium radiation. When strong lines of each constituent are resolved, however, it is possible to make a semi-quantitative estimate of their relative proportions from a series of powder photographs of synthetic mixtures of known composition, although the Geiger spectrometer is more convenient for this purpose, and will yield results of greater accuracy, if sufficient material is available.

The X-ray diffraction powder method is not very sensitive towards minor constituents in a mixture because the relative intensity of each set of lines in the composite pattern depends not only on the relative proportion of each crystalline phase but also on the relative strength of each pattern under normal conditions. Thus, the strongest lines from a trace of an impurity that would give a strong pattern if it were the only substance present may be identifiable, whereas those from a much larger proportion of a substance normally giving a very weak set of lines may not be observed. Depending, therefore, on the substances involved, the mass of one that can be detected in the presence of another varies from 1 per cent or less in the case of the simpler inorganic compounds to 5 or 10 per cent (or more) for complex and less symmetrical structures containing only light atoms such as carbon, nitrogen, and oxygen. Consequently, if the constituents in smaller proportion in a mixture are to be identified it may be necessary to effect at least a partial separation before obtaining the powder pattern. In narcotics seizures, for example, it is important that the diluent (usually lactose) be removed if the narcotic and possible adulterant (frequently quinine) are to be recognized. The importance of this point already has been dramatically illustrated in the literature (14). On the other hand, the insensitivity of the powder method

to small amounts of impurities is an obvious advantage (compared, for example, with a melting point determination) if only the identification of the major constituent of the sample is required. As may be inferred, of course, the absence of lines characteristic of a particular substance does not prove that the substance is not present in a given sample; it may be there in too small a proportion for its pattern to appear on the film in the time required even for an overexposed photograph of the diffraction lines due to the other constituents.

In assessing the value of the X-ray diffraction powder method for the identification of narcotics it is important to recognize that it is not simply another method of carrying out a chemical analysis. The X-ray method, when successful, identifies a specific crystalline phase uniquely. It thus completely characterizes the phase with all those properties that may previously have been determined by other methods, and, therefore, much more is known immediately about the unknown than would be possible by ordinary analytical procedures without a protracted investigation. This is both a strength and a weakness of the method depending on the point of view. For example, if the chemical constitution is all that is desired, without regard to degree of hydration or polymorphism, the method may be considered as too sensitive because different polymorphic forms and different hydrates of the same compound give different powder patterns. Consequently, if an identification is not made, a particular substance cannot be eliminated as a possibility unless the patterns of all possible polymorphs and hydrates have been included in the search. The same situation exists in the case of compounds with the same empirical formula because, if the molecular structure is different, the crystal structure also is different, and even the powder patterns of stereochemical isomers are not identical. On the other hand, identical powder patterns are obtained from both the *d* and *l* forms of optical isomers. This limitation obviously becomes important in any attempt to use the X-ray diffraction powder method in studies involving the relative addiction potential of the two antipodes. Furthermore, it follows that the powder pattern of the *dl* racemoid must be the same as that of the *d* and *l* isomers if crystallization occurs under conditions resulting in the formation of a mixture of separate crystals of the *d* and *l* forms. If, however, the *dl* racemoid crystallizes as such, its powder pattern may, but probably will not, be identical with that given separately by the antipodes.

For the complete and positive identification of pure substances in the crystalline state the X-ray diffraction powder method possesses certain unique features. It is apparent from the foregoing discussion, however, that it is not always self-sufficient; it is frequently most powerful when used in conjunction with other techniques. The outstanding advantages of the method, particularly for the identification of narcotics, are that it is relatively easy to employ, it is non-destructive and can be applied to very small specimens, the time required compares favourably with other analytical procedures, and a permanent record in the form of a photograph or a spectrometer chart is obtained automatically. Commercial X-ray diffraction units, particularly those with sealed tubes, are not difficult to operate, and skill in preparing and mounting samples is acquired easily. The X-ray diffraction powder method is an important and very desirable addition to any analytical laboratory.

Acknowledgements

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The Application of Conformational Analysis to Morphine Derivatives

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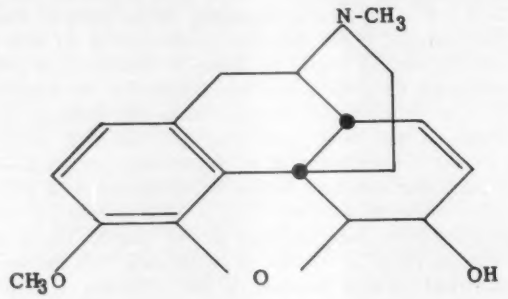
The concept of conformational analysis has provided the organic chemist with a powerful tool in the investigation of stereochemical problems. This concept has been introduced by Pitzer (1)[1] and by Hassel (2) and has been popularized by Barton, who admirably reviewed the subject primarily with regard to steroid and triterpenoid chemistry (3). Several important ideas relevant to the fine stereochemistry of alicyclic systems have been contributed by Johnson (4). The value of conformational analysis, and its validity in explaining the stereochemistry of certain natural and synthetic products, are being recognized by many other workers. Thus it has been possible to employ the ideas implied by conformational analysis in *a priori* decisions regarding the spatial arrangements to be expected in products of various synthetic investigations, e.g., in the total synthesis of steroids (6, 7) and in the interpretation of the stereochemistry of various natural products (7, 8). Conformational analysis has been employed in alkaloid chemistry to correlate the steric relationships between the various tropane alkaloids (9, 10).

The reader who wishes to familiarize himself with the basic ideas and extensive utility of conformational analysis in cyclohexane chemistry is referred to Barton's review of the subject (3). In this article certain points in the chemistry of morphine and its derivatives will be discussed in terms of the probable conformations of the substituents concerned. It will be seen that there is not sufficient data to prove unequivocally all of the conclusions reached and to extend them further to other reactions of these alkaloids. However, the general conclusions implied by this method open a fruitful field of inquiry by chemists who may be interested in supplying some of the missing evidence. To obtain part of this evidence, certain investigations are in progress in this laboratory. We beg to be forgiven for the speculative nature of a large portion of this article. These speculations will be justified if they encourage other workers to seek similar evidence in this field.

Morphine (I) consists of a tetracyclic ring system in which one of the rings (A) is aromatic, two of the carbocyclic rings (B and C) form a fused *cis*-octalin system and ring C and the nitrogen-containing ring D are fused in the form of a *trans*-octahydroisoquinoline ring system. The evidence for this steric arrangement has been reviewed in an article which recently appeared in this *Bulletin* (11).

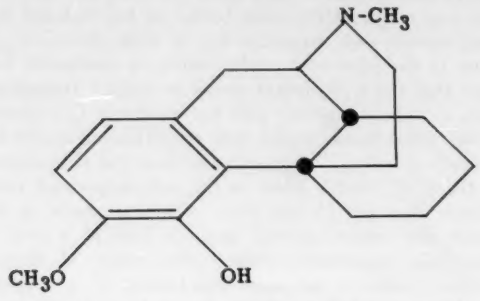


I

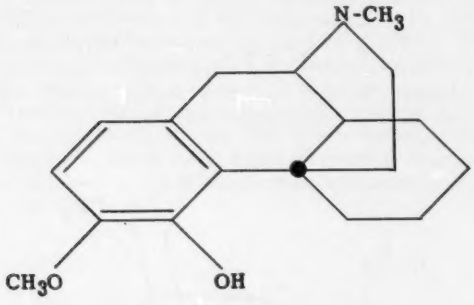
Clearly, the presence of the double bonds in the alicyclic rings, B and C, prevent these rings from attaining the true chair or boat conformations which are possible in a similar fully hydrogenated ring system. For this reason, care must be exercised in drawing the same conclusions in the cyclic system of morphine as are reached on the basis of conformational analysis of saturated systems. The same caution must be noted also in the case of compounds of the dihydromorphine series (double bond in ring C is reduced), for here also we are dealing not with a true decalin system but with a system fused to an aromatic ring through ring B. The latter, then, still shares a double bond with the aromatic ring A at their juncture. It is believed, nonetheless, that the conclusions reached below are sound. With the above qualifications in mind, let us turn to the fine stereochemistry of morphine and its derivatives from the viewpoint of conformational analysis.

Neglecting, for the moment, the oxide ring of morphine, structures II and III represent the structures of tetrahydrodesoxycodeine and β-tetrahydrodesoxycodeine, respectively.

[1] Figures appearing in parentheses throughout the text refer to the numbered references listed at the end of this article.

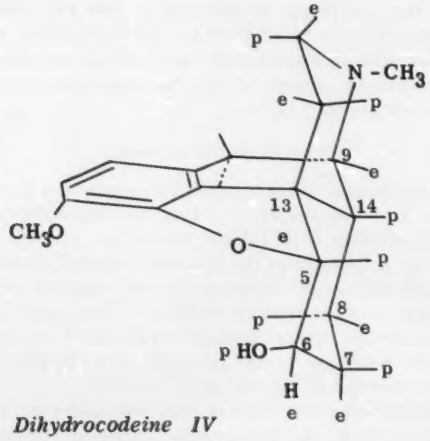


II



III

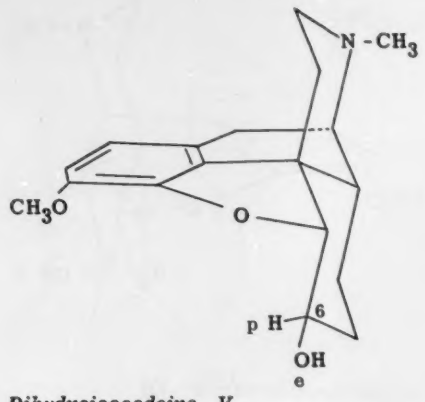
In tetrahydrodesoxycodeine (II) we have the steric arrangement present in morphine itself, i.e., rings B and C are *cis*-fused, while structure III is representative of the abnormal arrangement present in certain synthetic or degradation products, in which rings B and C are *trans*-fused, e.g., in β-dihydrothebainone.



Dihydrocodeine IV

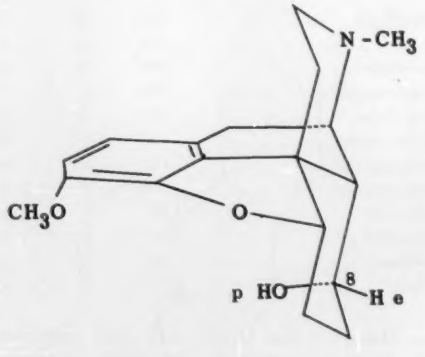
OXIDATION OF ALCOHOLS IN THE MORPHINE SERIES TO KETONES

Rapoport and coworkers (12) have found that certain alcohols of the dihydrocodeine series are readily oxidizable to ketones by means of the benzophenone-potassium *t*-butoxide system, whereas certain isomeric compounds are, for all practical purposes, not oxidized. Thus, it was found that dihydrocodeine (IV) in which the hydroxyl group at C_6 is polar, affords dihydrocodeinone in 83 per cent yield, while dihydro*iso*codeine (V), its C_6 epimer (equatorial hydroxyl group) gives this ketone in only 3 per cent yield.

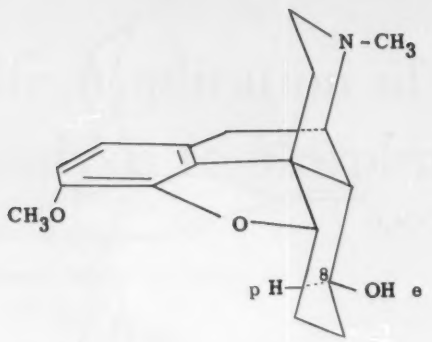


Dihydroisocodeine V

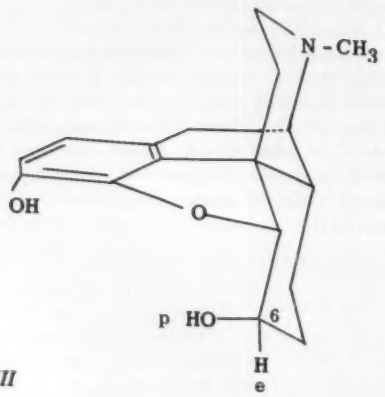
Similarly, dihydro*allopseudo*codeine (VI) (polar hydroxyl at C_8) is oxidized to dihydro*pseudo*codeinone in 40 per cent yield but dihydro*pseudo*codeine (VII) (equatorial hydroxyl at C_8) is recovered unchanged under the conditions of the oxidation. Dihydromorphine (VIII) with a polar hydroxyl group at C_6, is oxidized analogously to dihydromorphinone in 71 per cent yield. These experimental results are in accord with the general experience in the preferential oxidation of polar alicyclic alcohols (cf. 3).



Dihydro-allopseudocodeine VI



Dihydropseudocodeine VII



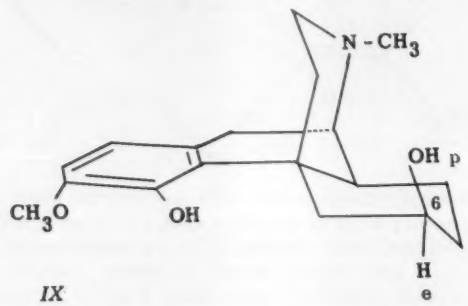
VIII

Table I summarizes the conformations of the respective substituents in various compounds of the morphine series.

TABLE I

Compound	*Substituent*	*Position*	*Conformation*
Codeine	OH	6	p
*Iso*codeine	OH	6	e
*Pseudo*codeine	OH	8	e
*Allopseudo*codeine	OH	8	p
Dihydrocodeine	OH	6	p
Dihydro*iso*codeine	OH	6	e
Dihydro*pseudo*codeine	OH	8	e
Dihydro*allopseudo*codeine	OH	8	p
α-chlorocodide	Cl	6	p
β-chlorocodide	Cl	8	e
Bromocodide	Br	8	e
Iodocodide	I	8	e

Since Rapoport and Payne (13) have unequivocally proved the stereochemical relationship between the C_5-O $_{ether}$ bond and the C_6-O $_{hydroxyl}$ bond in codeine to be *cis*- with respect to each other and since the only way one may construct the ether bridge in the *cis*-fused B,C ring system (see structure I), is with the C_5-O $_{ether}$ bond in the equatorial conformation, it necessarily follows that the C_6-hydroxyl group is polar.[2] *Iso*codeine, then, must be the isomer with the equatorial C_6-hydroxyl group. These facts coupled with the oxidation results for the corresponding dihydro-isomers show that the presence of the C_7-C_8 double bond in the unhydrogenated compounds does not change their molecular shape to the extent that conformational analysis fails as a tool of diagnostic importance. Direct observation of Barton models[2] leads to the same conclusion. If it may be equally assumed that a C_6-C_7 double bond in the morphine ring system will not upset the conformational applecart, then the assignments made for *pseudo*codeine and *allopseudo*codeine in table I are also correct on the basis of the oxidation data for the respective dihydro-derivatives. Definitive evidence regarding this point could easily be obtained through oxidation studies directly with *pseudo*codeine and with *allopseudo*codeine.



IX

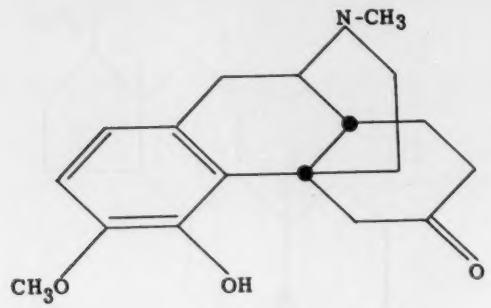
Further oxidation experiments in this field indicate that in β-dihydrothebainol (IX), the C_6-hydroxyl group is polar since this compound was oxidized to β-dihydrothebainone by means of the benzophenone-potassium *t*-butoxide system (14).

Reduction of Ketones

Sufficient data has accumulated to justify the generalization made by Barton (3) that for non-hindered ketones, reduction with lithium aluminium hydride gives a greater proportion of the equatorial alcohol. Reduction with alkoxides gives more of the polar alcohol than is obtained by other methods (although this epimer is not necessarily the major product) with the exception of catalytic reduction in the presence of acid. The latter method usually affords the polar alcohol.

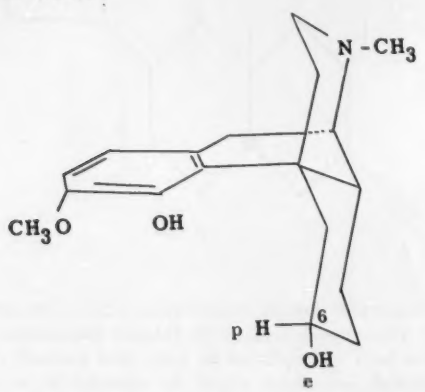
Dihydrothebainone (X) is reducible under a variety of conditions to the two possible epimeric dihydrothebainols (15, 16, 17).

[2] We are grateful to Dr. D. H. R. Barton, who enabled us to obtain a set of the models which he designed. These models are very helpful in clearly illustrating the spatial relationships in alicyclic compounds.

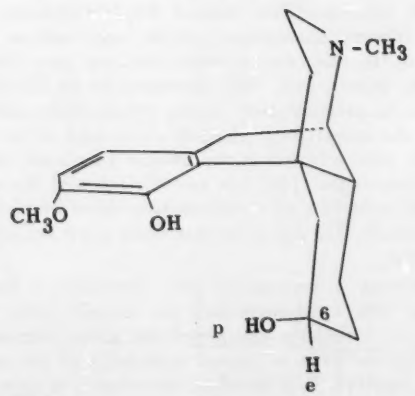


X

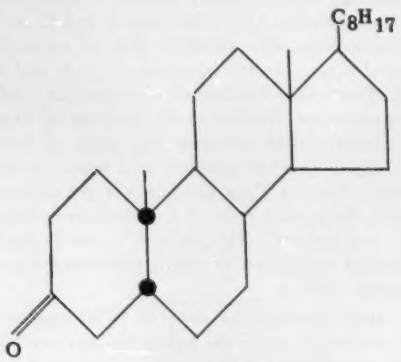
Dihydrothebainol A is obtained by electrolytic reduction of dihydrothebainone or by reduction with sodium amalgam. Dihydrothebainol B is obtained by reduction of the ketone in the presence of a platinum catalyst and hydrochloric acid. It might be argued from the following analogy to the steroids that dihydrothebainol A is the isomer in which the C_6-hydroxyl group is equatorial (XI) whereas in the B isomer the corresponding group is polar (XII).



XI

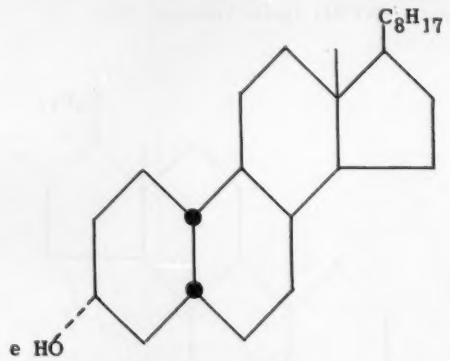


XII

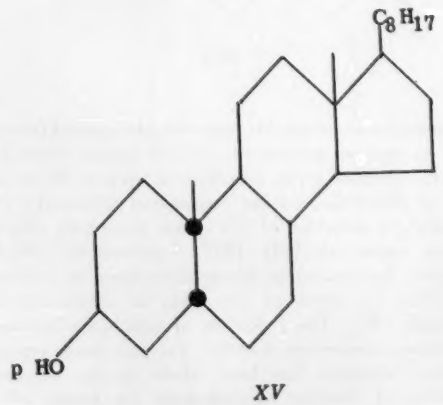


XIII

Coprostanone (XIII) (rings A and B *cis*-fused) on reduction with platinum in neutral solution gives *epi*coprostanol (XIV) (equatorial hydroxyl) while reduction in acid solution gives coprostanol (XV) (polar hydroxyl). Coprostanol upon treatment with sodium alkoxide at 180° is converted to *epi*coprostanol, indicating that in the presence of alkali the stable isomer is the one bearing the equatorial alcoholic function.



XIV

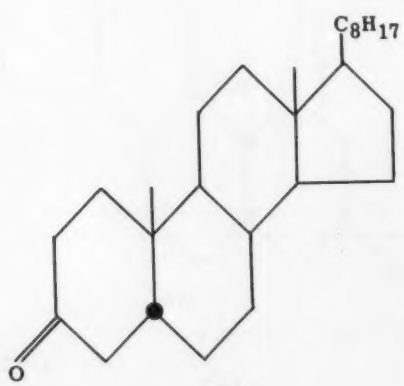


XV

This analogy is particularly attractive since behavior of dihydrothebainone (X) with rings B and C *cis*-fused, upon bromination, also parallels that of coprostanone (XIII) and other steroids in which rings A and B are *cis*-fused. Thus, bromination of coprostanone yields 4-bromocoprostanone. Neglecting the product of bromination of dihydrothebainone with one mole of bromine, which results in the introduction of a bromine atom in the aromatic ring (at C_1, a position not germane to this discussion), the second mole of bromine effects bromination at C_5 and not at C_7. This, indeed, forms the basis for the method of cyclization of dihydrothebainone to dihydrocodeinone (18).

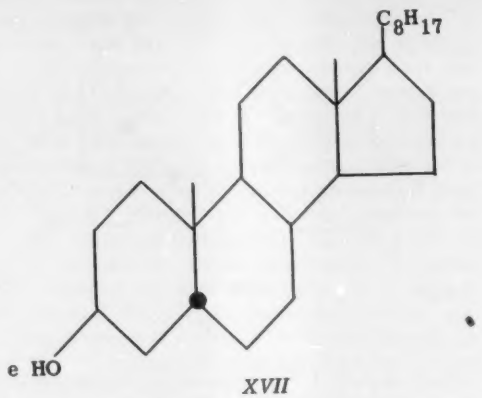
If the above analogy to steroids is warranted, then dihydrothebainol A bears the equatorial hydroxyl group while dihydrothebainol B has a polar alcoholic function. It would therefore be expected that the B isomer would be oxidized to dihydrothebainone much more readily than the A isomer by means of the benzophenone-potassium *t*-butoxide system.

Coprostanone upon reduction with lithium aluminium hydride affords the 3α-alcohol (XIV) (equatorial hydroxyl) in 94 per cent yield and the 3β-epimer (XV) (polar hydroxyl) in only 4 per cent yield. Similarly, cholestanone (XVI) gives 91 per cent of the 3β-alcohol (XVII) (equatorial hydroxyl) and 4 per cent of the 3α-isomer (XVIII) (polar hydroxyl) (19).

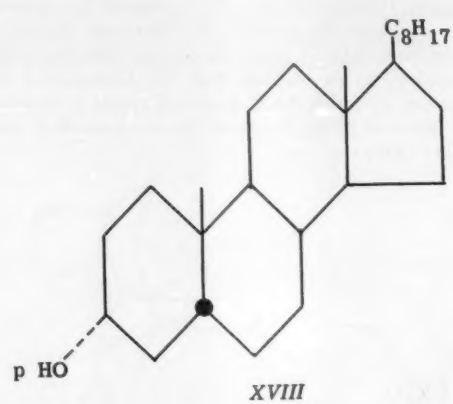


XVI

Aluminium *iso*propoxide reduction, the method favoured when an optimal amount of polar alcohol is desired, of dihydrocodeinone gives, nevertheless, up to a 94 per cent yield of dihydro*iso*codeine (equatorial hydroxyl) (20) but catalytic reduction of this ketone gives only dihydrocodeine (polar alcohol) (21). Furthermore, dihydrocodeine is isomerized to dihydro*iso*codeine in 30-65 per cent yield by means of potassium or aluminium *iso*propoxide (20). The reduction of codeinone by means of lithium aluminium hydride has not been reported although reference has been made to the successful oxidation of codeine to codeinone by means of an



XVII



XVIII

alkoxide-acceptor ketone combination (22). The reduction of 1-bromocodeinone with lithium aluminium hydride has been accomplished by Gates and Tschudi (14) but although *iso*codeine might be expected to be the major product on the basis of the foregoing discussion, codeine (polar hydroxyl) was obtained. Mr. Dov Elad, in this laboratory, has reduced dihydrothebainone with both lithium aluminium hydride and sodium borohydride. In this case epimeric mixtures were obtained but the isomer, m.p. 142°, presumed to be dihydrothebainol A, predominated in the borohydride reduction while the isomer, m.p. 166-168°, presumed to be the B isomer, predominated in the lithium aluminum hydride reduction. Gates (14a) has recently reported the stereospecific reduction of codeinone to codeine by means of borohydride. The reason for this result is not immediately apparent.

Flowsheet I summarizes the relationships between codeine and its isomers and the chlorocodides. Stork (23) has brilliantly interpreted the above interconversions on the basis of present knowledge of the mechanisms involved. It is therefore unnecessary to repeat the arguments here.

The Halocodides

Flowsheet I

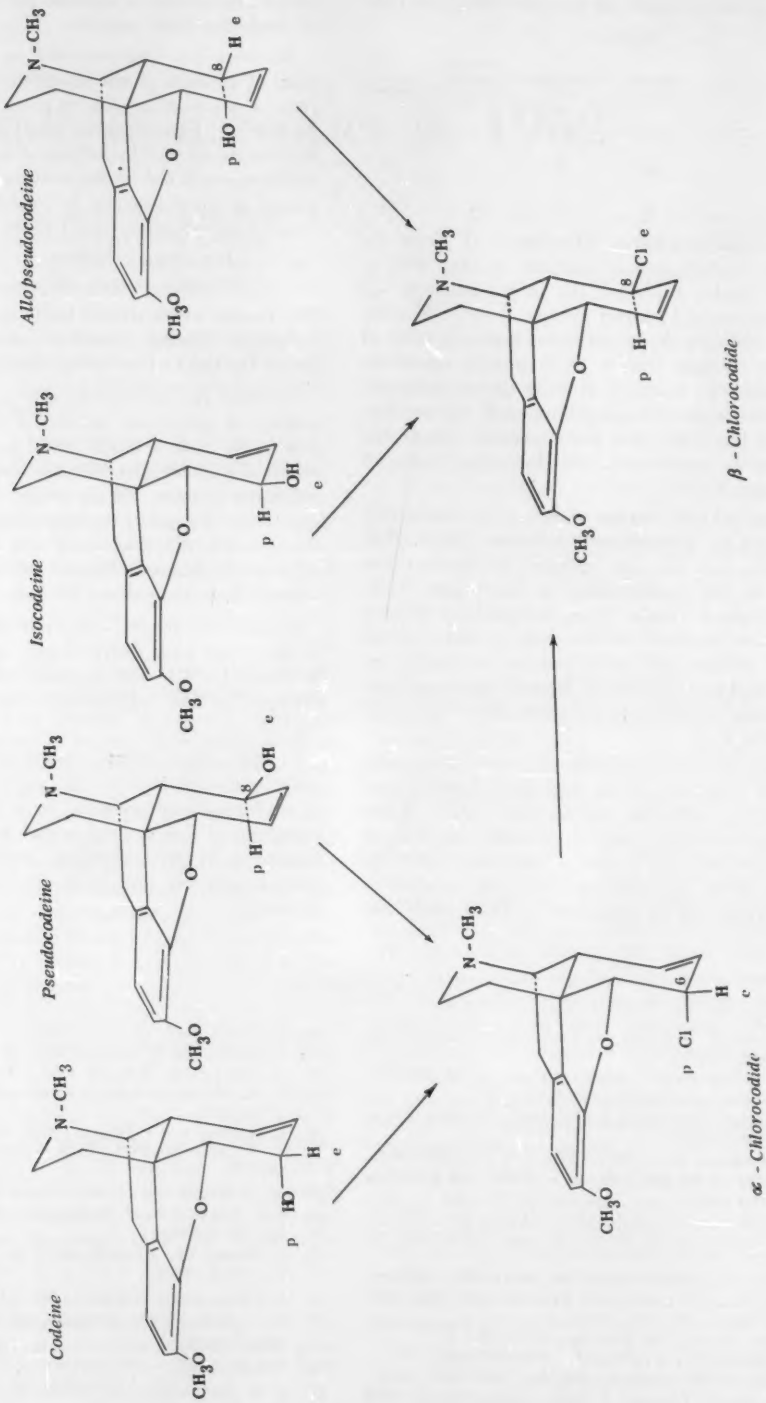


Table II summarizes the data obtained on the solvolysis of α- and β-chlorocodides in aqueous acetic acid (24).

TABLE II

Solvolysis of	*Isocodeine (e-OH)*	*Pseudocodeine (e-OH)*	*Allopseudocodeine (p-OH)*	*Total equatorial products*
	Per cent			
α-chlorocodide (p-Cl)	25	45	15	70
β-chlorocodide (e-Cl)	55	10	20	65

The significant conclusion from table II, from the viewpoint of conformational analysis, is that with α-chlorocodide (polar chlorine) the major products are those with equatorial hydroxyl groups. With β-chlorocodide (equatorial chlorine), again the major portion of the solvolysis products consists of those with equatorial hydroxyl groups. In no case is codeine (polar hydroxyl) formed in isolable amounts; α-chlorocodide (polar chlorine) itself, is less stable than β-chlorocodide (equatorial chlorine) and is converted to the latter by means of various reagents (25).

The fact that only one bromocodide and one iodocodide exist, having what is presumed to be the β-halocodide structure (26), may also be explained by the fact that the halogen in this conformation is equatorial. While in α-chlorocodide, a chlorine atom is capable of existing in the polar conformation, the bromine or iodine atoms due to their greater size would not be as readily accommodated and any α-isomer, if formed, apparently prefers to rearrange allylically to the more stable equatorial conformation at C_8.

The reaction of thionyl chloride with alcohols is much more complex than had at one time been believed and may proceed by different mechanisms (27). When further studies have been carried out with this reagent and the effect of reaction conditions has been better defined, it may be fruitful to repeat the work involved in the cycle summarized in flowsheet I. This would not only verify Stork's arguments in this regard (23) but would also permit a stepwise test of the *a priori* tenets of conformational analysis.

No work has been reported on the relative acylation rates of alcohols of the morphine series. A study of the rates of esterfication of a set of alcohols such as codeine, *iso*codeine, *pseudo*codeine and *allopseudo*codeine and the relative rates of hydrolysis of the esters would furnish additional evidence for the conformations of the hydroxyl groups in these isomers. It would be expected that the rates of esterification would be in the order:

*Iso*codeine>Codeine

*Pseudo*codeine>*Allopseudo*codeine

The reverse order should hold for the relative rates of hydrolysis. Similar orders of reactivities would be expected for the corresponding dihydro-derivatives.

It would also be interesting to note whether chromatography of polar and equatorial epimers in this series would give further experimental support for the generalization that polar alcohols are less absorbed than their equatorial isomers. We are aware of one case of clearcut separation of a pair of epimers which has been reported. As expected, dihydrocodeine was eluted readily from a column of alumina. Dihydro*iso*codeine had to be recovered from the column by means of dilute acid (20).

Regularities in the infra-red absorption of various alcohols and their esters should be observed when data is accumulated in the morphine series, in analogy, for example, to the regularities observed in the steroids (cf. 3).

In this article certain results in morphine chemistry have been evaluated by the application of the method of conformational analysis. It is believed that the implications of this concept would lead to important confirmations of stereochemical relationships if evidence were sought on this basis in the field of morphine chemistry.

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OFFICIAL

Legal trade in narcotics in 1952

The report of the Permanent Central Opium Board [1] to the Economic and Social Council on its work during 1953 [2] is on the agenda both of the ninth session of the Commission on Narcotic Drugs, in April 1954, and the eighteenth session of the Council. This report presents an over-all picture for 1952 of the production and consumption of narcotics, and of their licit traffic throughout the world as it is shown by the analysis of the statistics submitted to the Board by governments.

The reader will find below the main features included in the report of the Permanent Central Opium Board.

Present state of control

The main object of the control exercised by the Board over the licit movement of narcotic drugs is to prevent licitly produced substances of this nature from being diverted to illicit use. To this end, the statistics which governments are required to supply under the international conventions are scrutinized quarter by quarter with a view to verifying whether all narcotic drugs exported from one country to another duly arrive at their destination. In addition, the Board draws up, for each country and each substance, an annual balance-sheet of the quantities available and the quantities utilized, and so determines the balance available at the end of the year, which should correspond to the stocks declared by governments. The control also aims at ensuring that supplies, imported or manufactured, are kept within the limits calculated by the Board in accordance with the provisions of the 1931 Convention, on the basis of the estimates provided for therein.

Conversion of codeine into morphine

In its last report to the Economic and Social Council the Board noted that in 1951, for the first time, codeine had been converted into morphine, 26 kg. of codeine being used to produce 18 kg. of morphine. When asked for further details, the government of the country which reported the operation explained that the morphine had in fact merely been recovered from the residues of codeine manufacture.

[1] Document E/OB/9, United Nations, Geneva, 1953.

[2] For the report of the Permanent Central Opium Board on its work in 1951, see *Bulletin on Narcotics*, vol. IV, No. 2; for the report in 1952, see *Bulletin on Narcotics*, vol. V, No. 1.

Trends in the licit movement of narcotic drugs in 1952

1. Raw materials

(a) *Opium*

The principal countries which produce opium licitly —Turkey, India, Iran, USSR and Yugoslavia—have supplied the Board with statistics relating to their production as prescribed by the 1925 Convention. Only two countries—namely, Laos and Viet-Nam—have failed to supply figures and these are, in any case, countries of much less importance as opium producers.

According to these statistics, the following amounts in tons of raw opium were reported as produced during the years 1948-1952:

Country	*1948*	*1949*	*1950*	*1951*	*1952*
Turkey	380.2	10.4	184.8	357.8	463.6
India	342.2	220.0	230.7	526.7	349.7
Iran	21.3	199.7	480.9	32.2	130.6
USSR	75.0	76.0	85.7	93.8	104.3
Yugoslavia	21.5	0.5	19.2	22.0	12.1
Bulgaria	4.4	0.7	1.0	0.9	6.7
Laos and Viet-Nam ..	?	?	?	?	?
Other countries	0.1	—	0.5	—	—
Total (incomplete)	844.7	507.3	1,002.8	1,033.4	1,067.0

There are various possible reasons for the quite considerable variations in the declared production figures. Some of these reasons, such as changes in the acreage sown or fluctuations due to weather conditions, present no particular difficulty from the standpoint of control. There are others, however, which merit the Board's attention, in particular the fact that governments, instead of declaring actual production, declare the amounts bought from producers by State monopolies. The significance of such production figures therefore depends not only on the efficiency of the control exercised in the countries in question but also to a large extent on the proportion of the total quantity harvested which the government agencies decide to acquire.

All the leading producing countries have supplied the Board with all the statistics prescribed by the 1925 Convention in regard to the utilization of their opium. The fact, however, that the moisture content—and hence the weight—of opium changes considerably during the period between harvest and utilization greatly impairs the effectiveness of statistical control.

Of the statistics supplied by opium-producing countries, the ones which are most subject to independent

check are those of exports, as they can be compared with the reports which come in from importing countries.

Compared with the levels reached in 1950 and 1951 (751 and 754 tons, respectively), exports from the producing countries declined by one-third (to 511 tons) in 1952 owing to the reduction in exports to manufacturing countries (from 743 tons in 1951 to 482 tons in 1952). Exports to countries where opium is utilized for non-medical purposes showed an increase—from 11 tons in 1951 to 29 tons in 1952, but these exports now represent only a negligible proportion (6 per cent) of producers' total exports. The drop in exports to manufacturing countries has not been accompanied by a reduction in the manufacture of morphine; these countries have, in fact, drawn on their opium stocks or have made greater use of another raw material—poppy straw (see paragraph (b) below).

In recent years India has been the only producing country exporting opium licitly to countries (Pakistan and Ceylon) where it is utilized for purposes which are described as quasi-medical. In 1952, Iran also exported opium to Pakistan. Quasi-medical consumption of opium exists in India itself and there is non-medical consumption in Cambodia, in Laos and Viet-Nam, where it is met out of domestic production. In Thailand requirements for non-medical purposes appear to have been met for several years out of opium confiscated in the illicit traffic.

(b) *Poppy straw*

This raw material of morphine is not covered by the International Conventions on Narcotic Drugs. Most of the countries using it, however, notify the Board of the amounts used in manufacture and the amounts of morphine thus produced. In certain countries the whole poppy is used; in others only the capsule, which is richer in morphine: the yield varies accordingly.

The steady increase in the manufacture of morphine from this raw material continued in 1952, reaching the highest figure so far recorded, namely, 16.9 tons. The figure was only 11.7 tons in 1950, the last year previous to 1952 for which complete statistics were available; it then represented only 18 per cent of the total morphine manufactured. In 1952, this proportion had reached 22 per cent.

(c) *Coca leaves*

So far as the Board is aware, coca leaves are produced in four countries: Bolivia, Colombia, Indonesia and Peru.

Only Colombia and Indonesia, which are not the largest producers, send the Board figures of their production which, in 1952, amounted to 198 tons in Colombia and 17 tons in Indonesia. These two countries have also accounted for the quantities so produced: in Colombia, the leaves are chewed by the indigenous population; those produced in Indonesia are exported to cocaine-manufacturing countries.

The other two producing countries, Bolivia and Peru, have never sent statistics of their production to the Board. The extent of production in Peru can, however, be gauged from the estimates recently submitted by that country to the Secretary-General of the United Nations, according to which the average annual production from 1943 to 1949 was 7,500 tons. Neither Bolivia nor Peru declares the quantities of coca leaves chewed in its territory. The data supplied to the Board by these two countries normally refer only to their exports.

Such gaps make it impossible for the Board to exercise the control over this product which the 1925 Convention entrusted to it.

For coca leaves as for opium, the fullest statistics furnished by producing countries are therefore those of exports. In 1952, according to these statistics, 323 tons were exported to cocaine-manufacturing countries and 219 tons to Argentina, which is the only non-producing country where coca leaves are chewed. The increase in exports from the producing countries to cocaine-manufacturing countries which has been noted over the last two years may be attributed to the fact that, since 1948, manufacturers of cocaine have been making less and less use of crude cocaine from Peru as a raw material, so that in 1952 Peru exported none.

(d) *Indian hemp*

The Board has nothing to add to its observations on the subject made in its previous report.[3]

2. Manufactured drugs

(a) *Morphine*

Since the end of the Second World War, world manufacture of morphine has constantly increased from year to year. In 1952, production amounted to 75.7 tons, or 3.1 tons more than that reported in 1951, which did not include production in Czechoslovakia. That country's output in 1952 was 1.2 ton.

Not all the morphine-producing countries contributed to this increase, and in some the opposite tendency was observed. The main increases and decreases are as follows, in tons:

	1951	*1952*	*Difference*
Increase			
Hungary	6.6	8.7	+ 2.1
Italy	1.4	3.0	+ 1.6
Switzerland	2.5	3.9	+ 1.4
Federal Republic of Germany	5.7	6.9	+ 1.2
Yugoslavia	0.9	1.8	+ 0.9
Decrease			
United Kingdom	14.1	11.8	— 2.3
France	7.8	5.9	— 1.9
Japan	1.1	0.1	— 1.0
USSR	11.2	10.6	— 0.6

In 1952, 82 per cent of the morphine manufactured was subsequently converted into codeine (84 per cent in 1951), so that it is the demand for codeine which governs the manufacture of morphine, and it is the steady increase in that demand up to 1951 which accounts for the expansion of such manufacture. However, in 1952, for

[3] See *Bulletin on Narcotics*, vol. V, No. 1.

the first time since codeine was brought under international control, the manufacture of this drug declined. Should this trend continue, morphine manufacture may well prove to have reached its peak in 1952.

Morphine is also converted into other drugs such as diacetylmorphine, dionine, hydromorphone (dihydromorphinone) and products not covered by the international conventions; but such conversion absorbed only 8 per cent of the morphine manufactured in 1952 (10 per cent in 1951).

It follows that the amount of morphine remaining available for use as such represented 10 per cent of production in 1952 (against 6 per cent in 1951). This rise does not mean that the demand for morphine as such increased, but rather that stock levels were raised.

(b) *Diacetylmorphine*

Manufacture of this drug declined from 381 kg. in 1951 to 120 kg. in 1952. In the latter year it was manufactured in only five countries. They are, in order of volume of production, the United Kingdom (88 kg.), Belgium (16 kg.), Argentina (9 kg.), France (5 kg.) and Hungary (2 kg.).

Thus the steady drop in world production of this drug, which has been noted in recent years, became more marked in 1952 owing to the decline in production in the United Kingdom and the cessation of production in Italy, Sweden and the Federal Republic of Germany.

(c) *Codeine*

Codeine is the most important chemical derivative of morphine, both in respect of volume of production and of consumption. Since this drug was brought under international control, in pursuance of the 1931 Convention, production has steadily increased, reaching a total of 66.5 tons in 1951. In 1952, it declined, for the first time, to 63.8 tons. The figures for both 1951 and 1952 are incomplete: data are lacking for Czechoslovakia in 1951 and for Spain in 1952. The latest production figure declared by Czechoslovakia (for 1952) and by Spain (for 1951) was approximately one ton each.

(d) *Dionine*

World production of dionine rose steadily until 1949; since then it has varied rather considerably (4.7 tons in 1949, 3.6 tons in 1950, 6.2 tons in 1951 and 5.1 tons in 1952). The lack of figures for Czechoslovakia in 1951 and Spain in 1952 has very little effect on the world total, since the production of neither country is important.

(e) *Other derivatives of opium alkaloids* [4]

The figure for world manufacture of these drugs for 1952—namely, 1,156 kg.—is incomplete, the production in Spain (in 1951: 107 kg.) not yet being known.

Total production in 1951 amounted to 1,038 kg. The 1952 statistics cover a larger number of such drugs, several of which were recently brought under international control in pursuance of the 1931 Convention (article II) or the 1948 Protocol.

(f) *Cocaine*

World production of cocaine, which fell in 1950 to the lowest level yet recorded by the Board (1,284 kg.), subsequently rose to 1,515 kg. in 1951 and to 2,142 kg. in 1952. Production in the latter year, however, remained lower by nearly half than before the Second World War.

The increase in production in 1952 did not correspond to a higher demand for consumption, the latter remaining more or less the same as in previous years, but rather to an increase of stocks.

(g) *Synthetic narcotic drugs*

In 1952, for the first time, the Board had at its disposal statistics for a complete year in regard to synthetic narcotic drugs. In view of the fact that several countries had subjected for some years certain of these drugs to national control and supplied statistics on them, it is possible to some extent to analyse trends in their movement.

The most important of these drugs, as regards volume of production and consumption, is pethidine. Production of pethidine, which developed very rapidly, seems to have become stabilized in 1951 and 1952 at about 12 tons (12.2 tons in 1951 and 11.6 tons in 1952).

The production of methadone, which is second in volume, is declining. It fell from 521 kg. in 1951 to 381 kg. in 1952; but these figures are incomplete, since the Federal Republic of Germany, which is among the countries manufacturing this drug, did not bring it under control until 1953.

The other synthetic narcotic drugs (for example, phenadoxone and levorphan) are recent discoveries, and only since 1952 has the Board had approximately complete statistics. According to these statistics, the production of these drugs amounted to 282 kg. in 1952.

The question of diacetylmorphine

The Board and the Supervisory Body have for some years past been deeply concerned at the large quantity of diacetylmorphine passing into illicit consumption.

In general, this consumption is supplied from illicit sources, but so long as this drug is extensively used in medicine there is always the danger of supplies being diverted from the licit into the illicit market, and the risk of adding to the number of addicts continues.

The Board and the Supervisory Body have accordingly called the attention of governments repeatedly to the recommendation of the 1931 Conference that the use of this drug should be curtailed or brought to an end; and they have enlisted the co-operation of the World Health Organization.

The subject has indeed occupied the mind of the latter organization for some years, and at its Sixth Assembly the World Health Organization unanimously adopted a

[4] Namely, oxycodone, hydrocodone, hydromorphone, acetyldihydrocodeinone, dihydrodesoxymorphine, metopon, benzylmorphine, pholcodine, nalorphine, dihydrocodeine and acetyldihydrocodeine.

resolution recommending the abolition of the importation and production of the drug.[5]

The following table sets out the scale of licit consumption during the past six years in the countries to which the Permanent Central Opium Board and the Supervisory Body have particularly directed their attention in this respect. They are pleased to observe the diminution which has taken place during these years.

Consumption of diacetylmorphine per million inhabitants
(In kilogrammes)

Country	*1947*	*1948*	*1949*	*1950*	*1951*	*1952*
Finland	17.67	38.15	16.93	5.20	4.49	1.98
Italy	5.00	4.26	4.16	2.31	2.21	0.75
Sweden	4.12	1.88	2.02	2.29	2.41	1.56
New Zealand ..	3.33	2.72	2.13	1.04	2.06	1.03
Australia	3.30	4.68	4.30	4.52	5.25	2.85
United Kingdom	1.87	2.18	2.71	2.27	2.38	1.79

Consumption has also declined in countries other than those mentioned in the foregoing table, and in some countries it has stopped altogether. Indeed, the fall in the world consumption during the last two decades has been remarkable. In 1929, just after the 1925 Convention came into force, world consumption of diacetylmorphine was 2,651 kg.; by 1948, it had fallen to 657 kg.; and by 1952, it was further reduced to 266 kg.

In the Board's report for 1948, and in the introduction to the Supervisory Body's statement of estimates for 1949, twenty-four countries were listed which, at that time, no longer used diacetylmorphine at all. Since then, according to the statistics and estimates furnished to these two bodies, the following countries have also discontinued its use:

Afghanistan	Laos
Czechoslovakia	Panama
Ethiopia	Saudi Arabia
Germany (Federal Republic)	South Korea
Iceland	Switzerland
Indonesia	Thailand
Iran	Turkey
Israel	USSR
Jordan	Yugoslavia

Moreover, Australia, Sweden and the Union of South Africa have declared that they are now using up their stocks of this drug, after which its use will be terminated.

The Board and the Supervisory Body are gratified at these developments. The problem continues, however, to engage their full attention, and they are maintaining their close collaboration with the World Health Organization.

Retrospect: twenty-five years of international control

The Board was established in 1928 when the Convention of 19 February 1925 entered into force: 1953 is therefore the year of its twenty-fifth anniversary.

The Board feels that it would be of interest on this occasion to end its report with a brief review of the evolution of the narcotic drugs problem during the last quarter of a century. This evolution is remarkable both for the growth of the campaign against the use of narcotic drugs for non-medical purposes and for the results achieved thereby.

In 1929, the first year for which governments supplied the Board with the information prescribed in the 1925 Convention, the consumption of opium for non-medical purposes was permissible in eighteen countries and territories of Asia, and in most of these the sale to addicts was a monopoly of the State. During the years that followed, several of the governments concerned abolished their respective monopolies and prohibited opium smoking, so that in 1953 consumption for this and other non-medical purposes had ceased to be licit except in seven of these countries or territories, and the most important of these is now taking steps to bring such consumption gradually to an end with a view to total prohibition in 1959. The total quantity of raw opium used licitly for non-medical purposes amounted to 1,585 tons in 1929 and to only 166 tons in 1952.

Likewise, in 1929 world production of morphine amounted to 55 tons. In the light of studies made at the time, the League of Nations' Adisory Committee on Traffic in Opium and Other Dangerous Drugs concluded that an annual average of 15 tons of that drug had been finding its way into illicit traffic during the years 1925 to 1929. This estimate appears conservative when it is recalled that the average annual production fell by 25 tons during the years 1930 to 1935 without any shortage being felt on the licit market. Production has since increased steadily, reaching 75 tons in 1952, but practically all (90 per cent) of the morphine so produced is used for the manufacture of other drugs, and mainly for codeine and dionine which are little liable to produce addiction. The production of morphine for use as such fell from 13 tons in 1929 to 7 tons in 1952. Similarly, the production of cocaine, which amounted to 5,700 kg. in 1929, fell to 2,140 kg. in 1952; and here again no shortage was felt on the licit market. A fall which is even more striking is that in the licit production of diacetylmorphine (heroin), the drug most favoured by addicts; this shrank from 3,620 kg. in 1929 to 120 kg. in 1952.

Before the international control machinery was created traffickers and drug addicts were able to obtain supplies without great difficulty from licit manufacturers and traders. Today their access to such sources is barred, since the control imposed by the 1925 and 1931 Conventions extends over all licit dealings in narcotic drugs.

If, moreover, synthetic drugs had appeared on the scene before this machinery was set up, they would no doubt have given rise to the same abuses as the "old" drugs. The adoption of the Protocol of 19 November 1948 made it possible to bring these drugs also under the provisions of the 1925 and 1931 Conventions and thus meet that danger.

The success so far achieved cannot be attributed only to the activities of international bodies. The credit in the first place should go to the governments which have

[5] See *Bulletin on Narcotics*, vol. V, No. 3.

striven to achieve a common purpose and to build up the organization requisite for the establishment of international control over narcotic drugs.

The efforts of governments or of the international organizations would not in themselves have sufficed to bring about so great a change in the situation obtaining in 1929 if the governments or these bodies had acted independently of each other. Close collaboration between them was essential as was also the support of world public opinion.

These efforts will be no less indispensable in the future, both in consolidating the results so far achieved and in improving still further the national and international systems of control. As is evident from other chapters of this report, a considerable illicit traffic still exists and even appears to have recrudesced during the last three years; so that, while it has become increasingly difficult for traffickers to obtain supplies from licit sources, they have by no means ceased to operate. Since enormous profits are to be made from supplying narcotic drugs to addicts, traffickers are ever ready to exploit any weakness in control systems and do not hesitate to set afoot clandestine production. Despite the risks involved, such production will remain feasible until governments of the opium- and coca-leaf-producing countries and of certain manufacturing countries remove from their control systems those weaknesses which have been mentioned elsewhere in this report. Furthermore, the clandestine production of Indian hemp, which is the basis of hashish (or marihuana), continues to present a very serious problem.

The conclusion is inescapable that the success of international control measures rests in fact on the efficiency of national control systems, which in turn requires that the services which operate these systems should be provided with adequate means to carry out their task. So far as the Board is concerned it will not relax its efforts and will loyally assume such additional tasks as may reasonably be laid upon it.

Expert Committee on Drugs Liable to Produce Addiction

Fourth report

The Expert Committee on Drugs Liable to Produce Addiction held its fourth session in Geneva from 22 to 27 June 1953.

1. Resolutions of the United Nations Economic and Social Council

The committee noted the resolutions taken by the United Nations Economic and Social Council on 22, 27, and 28 May 1952,[1] particularly the resolution concerning the control of synthetic narcotic drugs, in which the Council thanked WHO and other bodies concerned for the vigilance they had exercised with regard to these substances and endorsed their recommendations. The committee was glad to learn that the Council had requested the Secretary-General of the United Nations to draw the attention of governments to the desirability of bringing synthetic addiction-producing drugs under national legislation (if this is not already their practice) as soon as such drugs appear.

2. General views on experimental and clinical work on addiction-producing drugs

The committee referred to the statement made at its second session [2] concerning the inadequacy of medical research on drug-addiction problems. However, the committee drew attention to, and commended the work done by, the Committee on Drug Addiction and Narcotics of the National Research Council, Washington, D.C., which promotes research, both governmental and private, on many aspects of addiction. At the same time, note was taken of the lack everywhere of any adequate means of ascertaining the incidence of addiction, including that arising from the legitimate medical use of potentially addicting drugs. The committee again recommended that governments be urged to consider the desirability of setting up, or adding to, facilities for investigating the various aspects of drug addiction, particularly because of the rapidly accumulating number of synthetic substances with morphine-like effect.

[1] United Nations, Economic and Social Council (1952) *Economic and Social Council, Official Records, Fourteenth Session, 20 May-1 August 1952, Resolutions, Supplement No. 1*, New York, p. 28 (document E/2332).

[2] *World Health Organization, Techn. Rep. Ser.* 1950, 21, 8 (section 6.5).

3. Morphine and its derivatives

1. *The structure of morphine*

The committee considered at length the various proposals for the best means of characterizing the structural configuration of morphine and chemically related substances. The suggestions are essentially of two types, the one basing the structure upon the phenanthrene and the other upon the isoquinoline nucleus. Each of these is scientifically correct and feasible for particular purposes. The committee was of the opinion, however, that the characterization based on phenanthrene is preferable for classification of addiction-producing drugs, since it permits of essential differentiation between (1) morphine and chemically morphine-like alkaloids, such as those described in the 1931 Convention as "the phenanthrene alkaloids of opium", and (2) the other opium alkaloids, papaverine, etc., which contain an isoquinoline but not a phenanthrene nucleus. Therefore, the Expert Committee on Drugs Liable to Produce Addiction recommended that the procedure now in use with respect to morphine and related alkaloids, namely, their description in relation to the phenanthrene nucleus, be continued in documentation on international control of addiction-producing drugs.

2. *The conversion of codeine and ethylmorphine into morphine*

The committee, recognizing that some degree of conversion of codeine to morphine had been accomplished, was of the opinion that there should be no relaxation in the control of codeine, and that, in the formulation of any future agreement concerning the control of this substance, the possibility of its conversion into morphine should be taken into account.

Furthermore, it was accepted that conversion of ethylmorphine to morphine should be possible with no greater difficulty than the conversion of codeine to morphine. Therefore, the statements with respect to control of codeine apply equally to control of diacetylmorphine.

3. *Morphine retard preparations*

The committee noted the many efforts that have been, and are being, made to prepare morphine for therapeutic use in a form which will prolong its effectiveness. It recognized the desirability of such an objective, if it can

be achieved with safety, but was of the opinion that the various means employed to bring about this result in no way affect the essential addiction liability of the morphine component. Therefore, the committee concluded that preparations of this type must be handled and controlled in all respects exactly as are other preparations of morphine.

4. *Situation regarding diacetylmorphine (heroin)*

The committee was gratified to learn of the action taken by the Sixth World Health Assembly in passing without dissent a resolution concerning the medical use of diacetylmorphine (heroin).[3] The committee was in complete accord with the principles set forth in this resolution, since they bring to a focus the recommendations made by the committee at its previous sessions concerning the abolition of diacetylmorphine from medical practice. The committee therefore expressed the hope that means would be found to implement this resolution speedily.

5. *N-allylnormorphine and analogous compounds*

The committee considered the notification of the Government of the USA with respect to N-allylnormorphine (nalorphine) and again reviewed the information available with respect to the activity and addiction liability of this drug. When administered alone, nalorphine produces dysphoria rather than euphoria and has not caused the appearance of tolerance or physical dependence. It will not relieve the abstinence syndrome nor sustain a morphine addiction, but will precipitate abstinence phenomena if physical dependence on morphine or morphine-like drug has been established. When administered with morphine, nalorphine seems to attenuate the development of physical dependence.

The committee also considered the conversion of nalorphine into a drug capable of producing addiction. Such a conversion, although possible, is so difficult, and the yield is so small, that it is impracticable and constitutes no risk to public health.

The committee was of the opinion that nalorphine cannot be considered either to be an addiction-producing drug or to be capable of conversion into an addiction-producing drug for the purpose of the Convention of 13 July 1931 for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs, as amended by the Protocol signed on 11 December 1946. Therefore, the Expert Committee on Drugs Liable to Produce Addiction recommended that its opinion with respect to N-allylnormorphine (nalorphine) be communicated to the Secretary-General of the United Nations.

The Committee considered further the notification of the Government of the USA with respect to diacetyl-N-allylnormorphine. On the basis of the information available, the committee concluded that the position of this substance was analogous to that of N-allylnormorphine.

6. 6-Methyl-Δ^6-*desoxymorphine*

Referring to the notification of the Government of the USA, the committee was of the opinion that 6-methyl-Δ^6-desoxymorphine, because it (1) produces morphine-like effects, (2) will suppress the abstinence phenomena of a known morphine addiction, and (3) will sustain a morphine addiction, must be considered an addiction-producing drug comparable to morphine, and that 6-methyl-Δ^6-desoxymorphine and its salts should fall under the régime laid down in the 1931 Convention for the drugs specified in article 1, paragraph 2, group I, sub-group (*a*). Therefore, the Expert Committee on Drugs Liable to Produce Addiction recommended that its opinion with respect to 6-methyl-Δ^6-desoxymorphine and its salts be communicated to the Secretary-General of the United Nations.

4. Synthetic substances with morphine-like effect

1. *General aspects*

The committee referred to the point of view expressed in the report of its first session [4] that compounds having a similar chemical configuration and belonging to the same chemical group as other whose addiction liability is already known must be suspected of having addiction-producing properties until the contrary be proved.

The committee confirmed this view and considered that governments should watch these compounds with extreme care and take appropriate action immediately on the discovery of addiction-producing properties in any one of them, as requested by resolution 436 (XIV) G of 27 May 1952 of the Economic and Social Council.

2. *Synthetic substances of methadone type*

Referring to the notification of the Government of the USA, the committee was of the opinion that: α-6-dimethylamino-4,4-diphenyl-3-acetoxyheptane (alpha-acetylmethadol); α-6-dimethylamino-4,4-diphenyl-3-heptanol (alpha-methadol); and β-6-dimethylamino-4,4-diphenyl-3-acetoxyheptane (beta-acetylmethadol)—because of the evidence submitted with the notification that they (1) produce morphine-like effects, (2) suppress abstinence phenomena of a known morphine addiction, and (3) sustain a morphine addiction—must be considered addiction-producing drugs comparable to morphine. These substances and their salts should accordingly fall under the régime laid down in the 1931 Convention for the drugs specified in article 1, paragraph 2, group I. Therefore, the Expert Committee on Drugs Liable to Produce Addiction recommended that its opinion with respect to α-6-dimethylamino-4,4-diphenyl-3-acetoxyheptane (alpha-acetylmethadol), α-6-dimethylamino-4,4-diphenyl-3-heptanol (alpha-methadol), and β-6-dimethylamino-4,4-diphenyl-3-acetoxyheptane (beta-acetylmethadol), and their salts, be communicated to the Secretary-General of the United Nations.

Furthermore, the committee referred to the notification of 15 February 1952 from the Director-General of

[3] See *Bulletin on Narcotics*, vol. V, No. 3.

[4] *Official Records, World Health Organization*, 19, 31, section 8.

WHO to the Secretary-General of the United Nations, in which it was stated that: 4,4-diphenyl-6-dimethylamino-heptanol-3 (otherwise known as 6-dimethylamino-4,4-diphenyl-3-heptanol); and 4,4-diphenyl-6-dimethylamino-3-acetoxyheptane (otherwise known as 6-dimethylamino-4,4-diphenyl-3-acetoxyheptane)—are capable of producing addiction and should fall under the régime laid down in the 1931 Convention for the drugs specified in article 1, paragraph 2, group I. The committee reiterated the decision set forth in the Director-General's notification and stated that, in its opinion, the above chemical names in that notification, as well as the respective trivial names, methadol and acetylmethadol, included the optical and other stereoisomers of compounds so designated.

The committee took note of information presented in regard to a preparation which is stated to be, in fact, a mixture of the hydrochlorides of 6-dimethylamino-4,4-diphenylhexanone-3 (a substance very closely related to methadone and differing from it only in the absence of one methyl group) and *p*-oxyphenylmethylaminopropanol. Tests on the addiction liability of this mixture, as well as of its methadone-like component, are to be undertaken; but the committee wished to point out that this preparation is of the type referred to in section 4.1 of this report. Consequently, it should be suspected of having addiction-producing liability until specific evidence becomes available.

3. *Synthetic substances of morphinan type*

The committee considered the evidence on the addiction liability and possible clinical usefulness of the dextrorotatory isomer of 3-hydroxy-N-methylmorphinan (dextrorphan), and the dextrorotatory isomer of 3-methoxy-N-methylmorphinan (dextromethorphan), which is the methyl ether of the former compound. It was concluded that each of these compounds had been demonstrated (1) to have no morphine-like action, (2) to lack ability to sustain a morphine addiction, and (3) to have exhibited no signs of addiction liability. Further, although some transformation of dextromethorphan (or dextrorphan) into a product with some analgesic activity is possible, this is sufficiently difficult, and the yield is so small, for it to be regarded as impracticable and to constitute no risk to public health. Therefore, the Expert Committee on Drugs Liable to Produce Addiction having considered the request of the Swiss Government to have dextrorphan and dextromethorphan exempted from the obligations of the international conventions on narcotic drugs, was of the opinion that such exemption should be granted in accordance with chapter 1, article 3, of the 1948 Protocol, and recommended that this opinion be notified to the Secretary-General of the United Nations.

The committee confirmed its opinion, formulated in its third report,[5] that racemorphan, racemethorphan, levorphan, and levomethorphan are addiction-producing substances. It emphasized the probable necessity for special precautionary measures, particularly with respect to the levorotatory isomers, if one or another of the dextrorotatory isomers comes into general use in place of codeine, because the procedure for making the dextrorotatory isomer involves the simultaneous production of an equivalent of the levorotatory isomer.

[5] See *Bulletin on Narcotics*, vol. IV, No. 3.

4. *Dithienylbutenylamines*

Referring to the notification of the Government of the USA, the committee was of the opinion that: 3-dimethylamino-1,1-di-(2′-thienyl)-1-butene; and 3-ethylmethylamino-1,1-di-(2′-thienyl)-1-butene—because they (1) produce morphine-like effects, (2) will suppress abstinence phenomena of a known morphine addiction, (3) will sustain a morphine addiction, and (4) will cause the development of a morphine-like addiction—must be considered as addiction-producing substances comparable to morphine, and that these substances and their salts should fall under the régime laid down in the 1931 Convention for the drugs specified in article 1, paragraph 2, group I. Therefore, the Expert Committee on Drugs Liable to Produce Addiction recommended that its opinion with respect to 3-dimethylamino-1,1-di-(2′-thienyl)-1-butene, and 3-ethylmethylamino-1,1-di-(2′ thienyl)-1-butene, and their salts, be notified to the Secretary-General of the United Nations.

The attention of the committee was drawn to a third dithienyl derivative, 3-diethylamino-1,1-di-(2′-thienyl)-1-butene, now being marketed for use in veterinary medicine. This compound has been shown to be so closely similar in its pharmacological properties to the dithienyl derivatives referred to above that, in the opinion of the committee, 3-diethylamino-1,1-di-(2′-thienyl)-1-butene must also be considered as having addiction liability. Furthermore, the committee was of the opinion that the closest watch should be kept upon the development of new dialkyl-dithienylamines because those so far examined are so closely similar in their properties as to make the group of dialkyl-dithienylamines as a whole suspect with respect to addiction-producing properties.

5. International non-proprietary names

The committee noted the progress made in the procedure for selection of international non-proprietary names. It desired to emphasize the need for selecting such names for those substances which will come under international control, if possible, at least as soon as such control is instituted. It suggested that the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations should be requested to consider, in all its aspects, the question of the speedy selection of non-proprietary names for addiction-producing substances.

A list of proposed international non-proprietary names for addiction-producing drugs is given as an annex.

6. Mastication of the coca leaf

The committee considered again the problem of coca chewing and had drawn to its attention evidence on the

absorption of cocaine during the chewing process. It was pointed out that there is a wide variation from individual to individual in the amount of cocaine ingested by the coca chewers, just as there is among individuals who take the pure alkaloid for non-medical purposes. The term cocainism is applicable to the latter and, in the opinion of the committee, coca chewing (cocaism) must be considered a form of cocainism.

The present statement in no way modified the opinion expressed in the third report.[6]

7. Cannabis sativa L.

The committee was pleased to note that the elimination of cannabis preparations had already begun by national action, following the opinion expressed in its third report that "there is no justification for the medical use of cannabis preparation".

The committee expressed its agreement with the action taken by the Commission on Narcotic Drugs at its eighth session to the effect that the term "Indian hemp" should be replaced by the term "cannabis", as proposed by the representative of the World Health Organization. Furthermore, it was of the opinion that the definitions for cannabis and its preparations should be revised on the basis of the presence of active principles.

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[6] See *Bulletin on Narcotics*, vol. IV, No. 3.

ANNEX

Non-proprietary names for internationally controlled addiction-producing drugs

The following international non-proprietary names have been proposed for addiction-producing drugs under international control:

Oxycodone	for	dihydro-oxycodeinone (eucodal, etc.)
Hydrocodone	for	dihydrocodeinone (dicodide, etc.)
Hydromorphone	for	dihydromorphinone (dilaudid, etc.)
Metopon	for	7-methyldihydromorphinone
Pethidine	for	1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester (demerol, dolantin, isonipecaine, etc.)
Ketobemidone	for	4-(3-hydroxyphenyl)-1-methyl-4-piperidyl ethyl ketone (cliradon, etc.)
Alphaprodine	for	α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine (nisentil, etc.)
Methadone	for	4,4-diphenyl-6-dimethylaminoheptanone-3 (physeptone, polamidon, etc.)
Isomethadone	for	4,4-diphenyl-5-methyl-6-dimethylaminohexanone-3 (not on the market)
Phenadoxone	for	4,4-diphenyl-6-morpholinoheptanone-3 (heptalgin, etc.)
Levorphan	for	L-3-hydroxy-N-methylmorphinan } both known as methorphan,
Racemorphan	for	dl-3-hydroxy-N-methylmorphinan } dromoran
Levomethorphan	for	l-3-methoxy-N-methylmorphinan } neither yet available
Racemethorphan	for	dl-3-methoxy-N-methylmorphinan } in trade

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SCIENTIFIC PUBLICATIONS ON NARCOTIC DRUGS FOR 1953

INTRODUCTION

The following bibliography has been prepared by the Secretariat and includes scientific publications on narcotic drugs which appeared during 1953, as well as a few which appeared earlier but could not, for various technical reasons, be included in the preceding lists published in the *Bulletin on Narcotics*. This bibliography has no claim to be complete, and information regarding books or articles not included in it would be gratefully received by the Division of Narcotic Drugs, Department of Social Affairs, United Nations Secretariat.

The bibliography has been arranged by subject in the following way:

Part I. General and reference works

Part II. Opium poppy, opium and drugs manufactured therefrom

A. Opium poppy, opium and opium alkaloids collectively considered

B. Morphine

C. Other phenanthrene alkaloids and derivatives of opium

D. Other drugs and substances derived from the opium poppy

Part III. The coca leaf and cocaine

Part IV. Cannabis and its derivatives

Part V. Synthetic drugs

A. General works

B. Pethidine and related compounds

C. Methadone and related compounds

D. Morphinan and morphine synthesis

E. Dithienylbutenylamines and miscellaneous synthetics

Part VI. Addiction to narcotic drugs

Part VII. Miscellaneous

Under each heading, publications are arranged alphabetically by author. Due to the nature of the sources available to the Secretariat for preparing this bibliography, several titles are given in translation only. They are preceded by an asterisk.

Part I

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Part VII

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